Pergamon

Tetrahedron 57 (2001) 4687–4689

TETRAHEDRON

A novel reaction of ninhydrin with chlorotrialkylsilane leading to ninhydrin dimers, and their X-ray structural analysis

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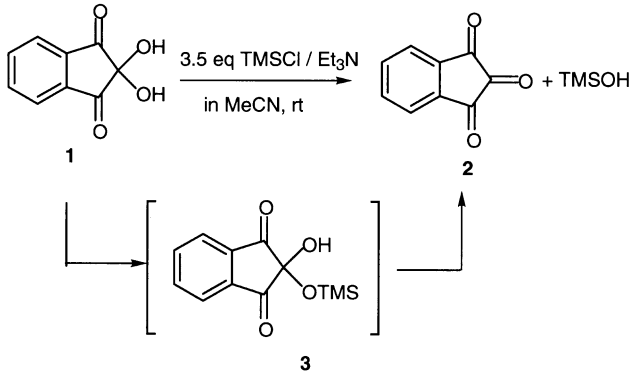
Received 9 March 2001; accepted 5 April 2001

Abstract—The reaction of ninhydrin with chlorotrialkylsilane gave a silylated ninhydrin dimer accompanied with bis(trialkylsilyloxy) derivatives; the dimeric structure was established by X-ray crystallographic analysis. The dimer is soluble in a nonpolar solvent and easily reproduces ninhydrin under mild conditions; thus it can be used as an equivalent molecule of ninhydrin for utilization as a detecting reagent.

Ninhydrin **1** has been found to be an extremely valuable reagent for the detection of an uncombined amino group in protein, peptides and amino acids.[1] Its special reactivity with amino acids was postulated by S. Ruhemann in 1910,[2,3] and ninhydrin has become the most common reagent for the chemical development of latent fingerprints.[4,5] However, the ninhydrin formulation suffers from certain disadvantages such as lower solubility in a nonpolar solvent, being soluble only in water or alcohol. Several groups have tried to modify the structure, and some remarkable results have been achieved; however, the synthesis requires multistep procedure.[1] We considered that a protecting technique of the hydroxyl group of ninhydrin would be a very simple and available method to improve the properties.

Many ketals of ninhydrin are already known for cyclic and aliphatic ketals; however, difficulty is inevitably incurred in their removal, and severe conditions such as strong acidic conditions are needed.[6–8] We tried to synthesize ninhydrin analogs which show both properties, namely, solubility in a nonpolar solvent and regeneration of ninhydrin under mild conditions, which ninhydrin analogs are eagerly sought for the detection of latent finger prints. Now we provide a new protecting technique of ninhydrin, which products show high solubility in a nonpolar solvent like hexane.

Yalpani and Wilke reported that the reaction of ninhydrin **1** with chlorotrimethylsilane (TMSCl) in the presence of tertiary amine smoothly and quantitatively gave indantrione **2**, and the intermediacy of hemiketal **3** is postulated (Scheme 1).[9] When we reinvestigated the reaction at room temperature, almost the same results were obtained. However, completely different results were obtained from the reaction on decreasing the reaction temperature. TMSCl (2.5 equiv.) was added dropwise to a THF solution of ninhydrin and triethylamine at −40°C, and the reaction mixture was stirred for 24 h at the same temperature. Precipitated salts were filtered off through a celite column (545) and the solvent was removed in vacuo. When the residual mixture was chromatographed on silica gel, two silylated materials were isolated in 15 and 55% yields (Table 1, entry 1), respectively. One compound was the bis(trimethylsilyloxy) derivative of ninhydrin, of which structure **4a** was characterized on the basis of spectral data. The other product was isolated as a yellow solid, and the Mass spectrum (FAB) exhibited a molecular ion peak (M+H) at 483.1262 calculated for $C_{24}H_{27}O_7Si_2$. This fact indicates that molecule was composed of two ninhydrin molecules and two TMS functions. The IR spectrum exhibited absorption at 1761 and



Scheme 1.

Keywords: ninhydrin; chlorotrialkylsilane; dimer; detecting reagent; ketal.
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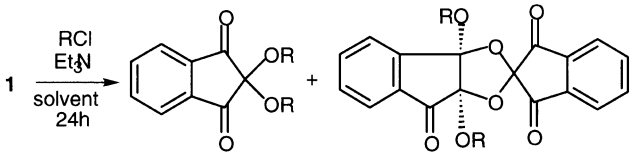
PII: S0040-4020(01)00394-5

Table 1. Silylation of ninhydrin with chlorotrialkylsilane



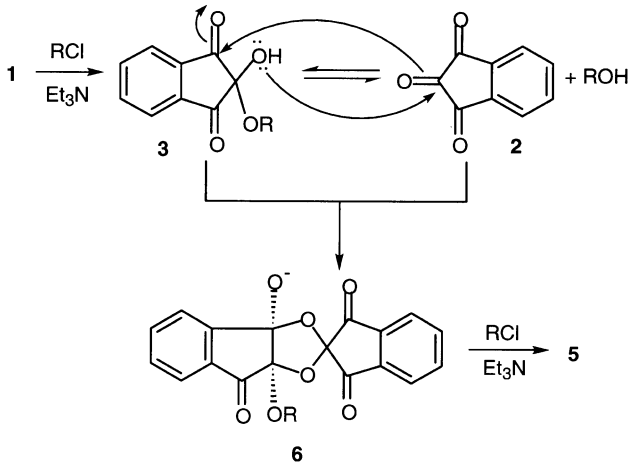
4a: R=TMS **5a**: R=TMS
4b: R=TES **5b**: R=TES
4c: R=TBDMS **5c**: R=TBDMS

Entry	R	Solvent	Temp.	Yields of 4	Yields of 5
1	TMS	THF	−40°C	15	55
2	TMS	THF	−20°C	21	54
3	TMS	THF	0°C	18	28
4	TMS	THF	20°C	0[a]	0[a]
5	TMS	DMF	−20°C	3	27
6	TMS	MeCN	−20°C	34	6
7	TES	THF	−20°C	10	28
8	TBDMS	THF	−20°C	12	11

[a] Indantrione was obtained

1734 cm^{-1} derived from the carbonyl group and absence of the hydroxy group. The ^1H NMR spectrum showed singlet peaks at 0.28 and 0.35 ppm owing to two non-equivalent TMS groups. The ^{13}C NMR exhibited singlet peaks at 97.5, 103.0, 109.3 ppm in addition to peaks derived from the TMS and aromatic groups. The dimeric structure **5a** was investigated on the basis of the spectral data. Finally, the structure **5a** was established by the single crystal X-ray structural analysis as shown in Fig. 1.

Table 1 shows the results of silylation under various conditions. Silylated compounds **4a** and **5a** were obtained in similar yields by the reaction at −20°C (entry 2); however, elevating the temperature resulted in lowering both chemical yields (entry 3), and only indantrione was obtained at



Scheme 2.

0°C (entry 4). THF was the best solvent for silylation, since the use of DMF or MeCN reduced the chemical yields (entries 5 and 6).

When we used other silylating reagents, chlorotriethylsilane (TESCl) or chloro(*t*-butyl)dimethylsilane (TBDMSCl), the corresponding silylated ninhydrins **4b–c** and **5b–c** were isolated as shown in Table 1, entries 7 and 8. In these cases, the chemical yields were less satisfactory, because the more bulky substituent around the silicon atom of the silylating reagent prevents the attack of the oxygen atom toward the silicon atom. The structures of **4b–c** and **5b–c** were determined on the basis of the spectral data.

The mechanism for the formation of ninhydrin dimer **5** can be explained as shown in Scheme 2. One of the hydroxy groups of ninhydrin is silylated, leading to hemiketal **3**, which exists in equilibrium with indantrione **2**. The lone

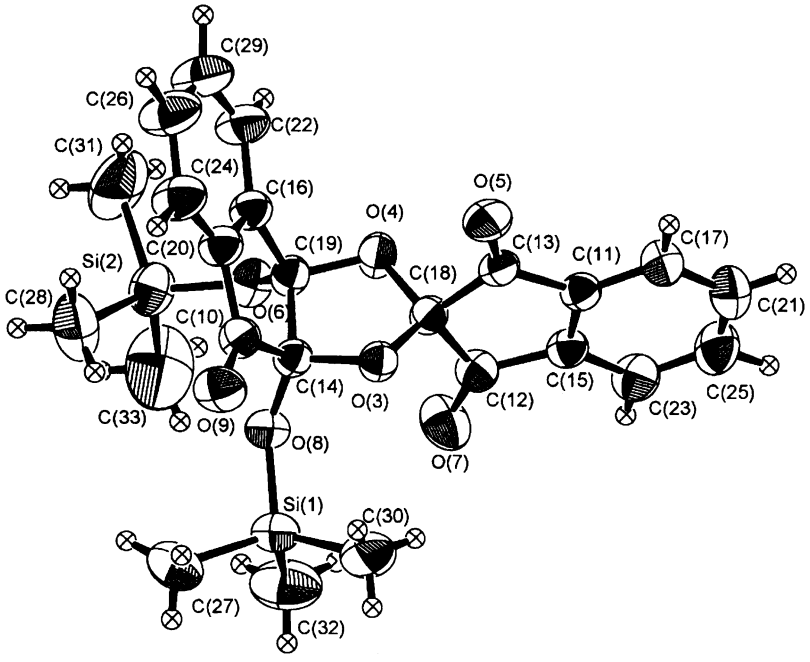


Figure 1. Ortep drawing of **5a**.

pair electron of the hydroxy group attacks the jammed carbonyl carbon of **2**; the reaction was subsequently followed by cyclization to dioxolane **6** and the dimeric structure was constituted. Finally, the second silylation of **6** leads to **5**. This is a characteristic reaction of chlorotrialkylsilane and the use of methyl iodide or ethyl iodide promoted not only the dimerization, but also the alkylation.[7,8]

The dimeric ninhydrin **5** is a stable solid and easily handled, and its solubility in a nonpolar solvent like hexane is high. The dimer **5a** (1.3 g) was soluble in 100 ml of hexane, which is equivalent to 5.3 mmol of ninhydrin. Furthermore, **5** is stable in hexane solution, and easily undergoes solvolysis on the addition of a small amount of alcohol, leading to ninhydrin. Actually, when alanine or alkylamines was added to the solution of **5a**, purple or yellow colored solution derived from Ruhemann's purple was obtained. In conclusion, the present reaction provides a new and convenient synthesis of ninhydrin analogs involving dimerization of ninhydrin and subsequent silylation.

1. Experimental

1.1. General

NMR spectra were recorded on $CDCl_3$ solutions on a JEOL GSX-400 and 500 operating 400 and 500 MHz, respectively, for ^1H and ^{13}C NMR spectroscopy. Chemical shifts are reported in parts per million (ppm) relative to TMS as an internal standard. UV Spectra were determined with a JASCO model V-570 UV/VIS/NIR spectrophotometer. IR Spectra were recorded on a JASCO FT/IR-230 spectrometer as KBr disks, unless otherwise noted.

1.2. General procedure for silylation of ninhydrin dimer 1

TMSCl (2.5 equiv.) was added dropwise to a THF solution of ninhydrin and triethylamine at −40°C and the reaction mixture was stirred for 24 h at the same temperature. Precipitated salts were filtered off through a celite column (545) and the solvent was removed in vacuo. When the residual mixture was chromatographed on silica gel, two silylated materials, **4a** and **5a**, were isolated in 15 and 55% yields (Table 1, entry 1), respectively. The structure **4a** was characterized on the basis of spectral data.[9] The structure of **5a** was established by X-ray structural analysis.

1.2.1. 3a,8a-Bis(trimethylsilyloxy)-3a,8a-dihydro-spiro-[1,3-dioxacyclopenta[*a*]inden-8-one]-2,2′-indene-1′,3′-dione 5a. Mp 92°C; IR (cm^{-1}, KBr) 1761, 1734; ^1H NMR ($CDCl_3$): δ 0.28 (s, 9H, Me), 0.35 (s, 9H, Me), 7.6–8.1 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 1.62, 1.89, 97.5, 103.0, 109.3, 124.0, 124.2, 124.3, 124.4, 130.7, 133.0, 136.5, 137.0, 137.1, 139.6, 140.0, 150.0, 191.4, 193.6, 193.7. HRMS (FAB) for $C_{24}H_{27}O_7Si_2$ (M+H) 483.1295, found 483.1262.

1.2.2. X-Ray structural analysis of 5a. Recrystallized from hexane, triclinic space group P-1, a=10.034 (2) Å, b=10.620 (1) Å, c=12.448 (5) Å, α=79.96 (2)°, β=77.89 (2)°, γ=83.83 (2)°, V=1273.7 (6) Å^3, Z=4, ρ=2.517 g.cm^{-3}, μ(Cu-Kα)=32.169 cm^{-1}, T=298 K. The structure was solved by direct methods and expanded using Fourier techniques. Final R and R_w were 0.054 and 0.084 for 4252 reflections.

1.2.3. 2,2-Bis-(triethylsilyloxy)-indan-1,3-dione 4b. Oil; IR (cm^{-1}, neat) 1759, 1734; ^1H NMR ($CDCl_3$): δ 0.62 (m, 12H, CH2), 0.90 (m, 18H, Me), 8.0 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 6.12, 31.3, 90.3, 124.5, 136.9, 139.1, 197.1. HRMS (FAB) for $C_{21}H_{35}O_4Si_2$ (M+H) 407.2074, found 407.2029.

1.2.4. 3a,8a-Bis(triethylsilyloxy)-3a,8a-dihydro-spiro[1,3-dioxacyclopenta[*a*]inden-8-one]-2,2′-indene-1′,3′-dione 5b. Mp 92°C; IR (cm^{-1}, KBr) 1760, 1731; ^1H NMR ($CDCl_3$): δ 0.75–0.90 (s, 12H, CH2), 0.90–1.00 (m, 18H, Me), 7.6–8.1 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 5.80, 6.13, 6.80, 6.94, 97.4, 103.1, 109.2, 124.0, 124.2, 124.2, 124.6, 130.8, 132.9, 136.5, 137.0, 139.7, 140.1, 149.9, 191.3, 193.7, 193.9. HRMS (FAB) for $C_{30}H_{39}O_7Si_2$.567.2234 (M+H), found 567.2188.

1.2.5. 2,2-Bis-(*t*-butyldiethylsilyloxy)-indan-1,3-dione 4c. Mp 67–68°C; IR (cm^{-1}, KBr) 1725; ^1H NMR (acetone-d_6): δ 0.11 (s, 12H, Me), 0.89 (s, 18H, *t*-Bu), 8.0–8.2 (m, 4H); ^{13}C NMR ($CDCl_3$): δ −3.44, −3.38, 18.16, 25.50, 90.3, 124.1, 136.5, 138.8, 196.6. HRMS (FAB) for $C_{21}H_{35}O_4Si_2$.407.2074 (M+H), found 407.2106.

1.2.6. 3a,8a-Bis(*t*-butyldimethylsilyloxy)-3a,8a-dihydro-spiro[1,3-dioxacyclopenta[*a*]inden-8-one]-2,2′-indene-1′,3′-dione 5c. Mp 192°C; IR (cm^{-1}, KBr) 1761, 1736; ^1H NMR ($CDCl_3$): δ 0.33–0.46 (s, 12H, Me), 0.89 (s, 9H, Me), 0.98 (s, 9H, Me), 7.6–8.1 (m, 8H); ^{13}C NMR ($CDCl_3$): δ −3.1, −2.8, −2.6, −2.3, 18.0, 18.6, 25.7, 26.07, 97.3, 103.4, 109.3, 124.0, 124.2, 124.3, 124.4, 130.7, 133.0, 136.5, 137.0, 137.1, 139.6, 140.0, 150.0, 191.4, 193.6, 194.0. HRMS (FAB) for $C_{30}H_{39}O_7Si_2$.567.2234 (M+H), found 567.2187.

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