Stereoselective Synthesis of Hexa- and Tetrahydroindolizin-7-ones through Cycloaddition of Pyridinium Methylides

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Received October 2, 1985

The 1,3-dipolar cycloaddition reaction of 4-((*tert*-butyldimethylsilyl)oxy)pyridinium methylides to electron-deficient olefins and acetylenes provides a convenient route to stereochemically defined 1,2,3-trisubstituted or 1,3-disubstituted derivatives of hexahydro- or tetrahydroindolizin-7-ones.

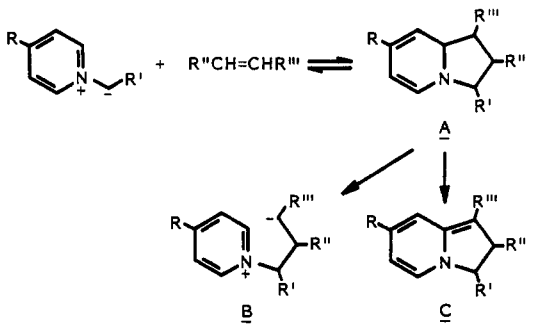
Although 1,3-dipolar cycloaddition reactions are highly stereo- and regioselective in the formation of five-membered heterocycles, the utility of these reactions is not always broad.[1] Typical is the cycloaddition of heteroaromatic *N*-ylides as azomethine ylide 1,3-dipoles. As this reaction is accompanied by loss of aromaticity of the heterocyclic ring, the primary cycloadducts frequently undergo secondary reactions.[2,3] Thus the cycloaddition of pyridinium methylide to an olefin affords adduct A, which isomerizes or decomposes with elimination of the pyridine nucleus via the zwitterion B or is dehydrogenated to C (Scheme I). Seoncdary reactions of A depend upon the electronic nature and steric size of the substituents R, R′, R″, and R‴. All cycloadducts of pyridinium methylides studied to date with olefins other than maleimides have been too labile to be isolated.[4-6]

In order to increase the stability of A and preserve its stereochemistry, we decided to formally reduce one of the double bonds in the fused dihydropyridine ring of A. This reduction could be accomplished by introducing a silyloxy substituent at the 7-position of A; desilylation should occur as soon as A is formed. This method would open a convenient route to a stereochemically defined hexahydroindolizin-7-one D (Scheme II).

Our approach to the required 4-(silyloxy)pyridinium methylides involved the preparation of 1-alkyl-4-(silyloxy)pyridinium salts by alkylation of 4-(silyloxy)pyridines and subsequent deprotonation. Although 4-((trimethylsilyl)oxy)pyridine could be alkylated with phenacyl bromide or α-bromoacetonitrile to form the corresponding pyridinium bromides E (R = Me, Scheme II), we were not able to isolate these salts or to generate 4-((trimethylsilyl)oxy)pyridinium methylides from them. The salts underwent ready desilylation to 1-alkyl-4-pyridones (F), which were presumably formed by rapid nucleophilic attack of Br^- on the silicon atom.

On the other hand, alkylation of 4-((*tert*-butyldimethylsilyl)oxy)pyridine (1) with phenacyl bromide, α-bromoacetonitrile, or methyl α-bromoacetate gave considerably more stable 1-alkyl-4-(silyloxy)pyridinium bromides 2–4. These salts were precipitated out of solution as they were produced, but they could not be isolated because of rapid desilylation to 1-alkyl-4-pyridones (F) upon exposure to air. However, we found that the salts 2–4 could be dehydrobrominated *in situ* with triethylamine, so the sequence of pyridinium salt formation, ylide generation, cycloaddition, and desilylation was performed in the same flask. For example, 1 was added to a solution of phenacyl bromide in dry acetonitrile, and the mixture was stirred at room temperature for 2 h under nitrogen.

Scheme I



Scheme II

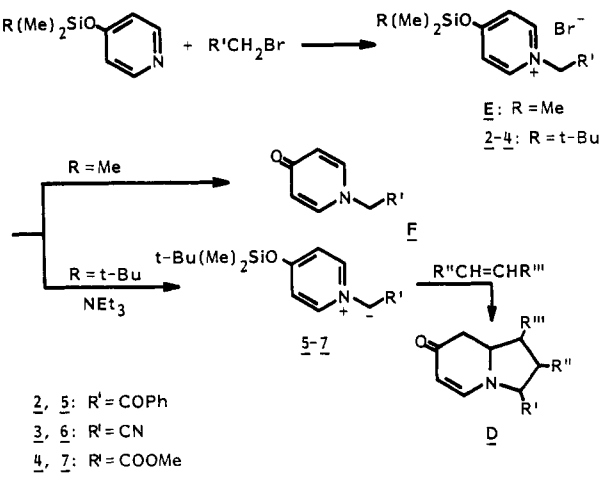
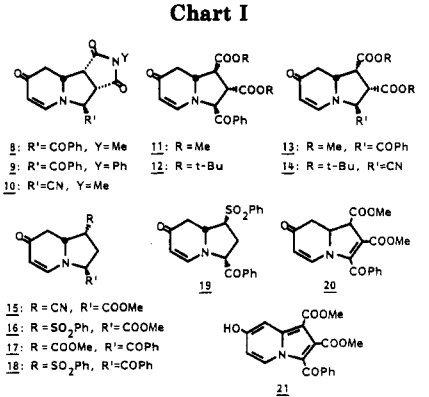


Chart I



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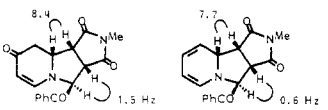
0022-3263/86/1951-1853$01.50/0

Table I. Cycloaddition of 4-((*tert*-Butyldimethylsilyl)oxy)pyridinium Methylides to Olefins

ylide	olefin	solvent[a]	reaction time, h: alkylation	reaction time, h: addition	product	yield, %[b]	mp, °C
5	*N*-methylmaleimide	AN	2	4	8	56	132–134
5	*N*-phenylmaleimide	AN	2	4	9	18	201–202
6	*N*-methylmaleimide	AN	15	2	10	51	166–169
5	dimethyl furmarate	AN	2	24	11	51	103–104
5	di-*tert*-butyl fumarate	AN	1	24	12	30	147
5	dimethyl maleate	DM	0.5	0.33	13	45	154
6	di-*tert*-butyl maleate	AN	19	2	14	30	191 dec
7	acrylonitrile	AN	14	5	15	23	oil
7	phenyl vinyl sulfone	AN	20	3	16	28	oil
5	methyl acrylate	DM	3	2	17	32	162–163
5	phenyl vinyl sulfone	AN	14	5	18 + 19 (2:1)	40	18: 238 dec 19: 240 dec

[a] AN = acrylonitrile; DM = dichloromethane. [b] Isolated yield based on 1.

Chart II



An equimolar amount of *N*-methylmaleimide and then a slight excess of dry triethylamine were added, and the mixture was stirred at room temperature for 4 h. Hydrolytic workup and chromatographic separation gave the pyrrolo[3,4-*a*]indolizin-8-one **8** as a single stereoisomer in 56% yield based on **1**. In this manner, reactions of pyridinium methylides **5** or **6** with *N*-methyl- or *N*-phenylmaleimide gave pyrrolo[3,4-*a*]indolizin-8-ones **8–10** as single stereoisomers (Chart I, Table I).

The major byproduct in the reactions with **5** was 1-phenacyl-4-pyridone, identified from the ^{1}H NMR spectrum of the crude reaction mixture. Possible pathways to this byproduct include (1) desilylation of **2** by attack of Br^- on the silicon atom in the alkylation step, (2) attack by triethylamine in the ylide generation step, or (3) desilylation of ylide **5**.

The stereostructures of **8–10** were assigned on the basis that the coupling patterns among methine hydrogens on the newly formed five-membered ring are similar to those of the endo cycloadducts of pyridinium methylides with maleimides.[2,4] The 3a,4-trans and 9a,9b-cis structures are confirmed by the small coupling constant J_{3a-4} (1.5 Hz) and by the larger coupling of J_{9a-9b} (8.4 Hz) as shown in Chart II.

The reactions of **5** and **6** with symmetrically substituted olefins such as dimethyl and di(*tert*-butyl) fumarates and maleates under similar conditions afforded stereospecific 1,2,3,7,8,8a-hexahydroindolizin-7-ones **11–14** (Chart I). Their structures were assigned on the basis of their ^{1}H NMR spectra, in which the coupling patterns among methine hydrogens on the five-membered ring were quite similar to those of the corresponding cycloadducts of isoquinolinium methylides.[2]

Reaction of ylide **7** with such unsymmetrically substituted olefins as acrylonitrile and phenyl vinyl sulfone gave single isomers **15–16** of 1,3-disubstituted hexahydroindolizin-7-ones (Chart I). On the other hand, while reaction of ylide **5** with methyl acrylate gave a single isomer **17**, its reaction with phenyl vinyl sulfone gave a mixture of two stereoisomeric hexahydroindolizin-7-ones **18** and **19** in a ratio of 2:1.[7]

(7) Compounds **15–18** are given structures of isomers derived from endo additions to the anti forms of **5** and **7** on the basis of comparison of their ^{1}H NMR coupling constants with those of isoquinolinium methylides.[3] Compound **19** was probably formed by isomerization of **18** through a betaine intermediate B.

Finally, ylide **5** reacted with dimethyl acetylenedicarboxylate under similar conditions to give a 1:1 mixture of two isomers of the tetrahydroindolizin-7-one **20** in 40% yield together with a trace of the dehydrogenated derivative **21**. Although the isomers **20** could not be separated, they are believed to be the double-bond-migrated *cis*- and *trans*-1,7,8,8a-tetrahydroindolizin-7-ones on the basis of the ^{1}H NMR spectrum of the mixture. These isomers were quantitatively dehydrogenated into the 7-hydroxyindolizine **21** by chromatography over silica gel through a long column.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IR A-702 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-40 or a JEOL FX-100 instrument, and ^{13}C NMR spectra were obtained on a JEOL FX-100 spectrometer at 25.05 MHz. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. Mass spectra were measured with JEOL JMS-01SG-2 spectrometer at 70 eV ionization energy. Elemental analyses were performed on a Hitachi 026 CHN analyzer. Thin-layer chromatography (TLC) was accomplished on 0.2-mm precoated plates of silica gel 60 F-254 (Merck). Visualization was with ultraviolet light (254 and 365 nm) and iodine. Silica gel 60 (Merck, 70–230 mesh) was used for preparative column chromatography. Solvents were evaporated with a Tokyo Rikakikai rotary evaporator type V.

Toluene was distilled from sodium metal. Both dichloromethane and acetonitrile were distilled from P_2O_5 under nitrogen and stored on 5-Å $^1/_{16}$ molecular sieves. Triethylamine was distilled and stored over KOH pellets.

4-((*tert*-Butyldimethylsilyl)oxy)pyridine (1). A solution of 4-pyridone (2.8 g, 0.03 mol), *tert*-butyldimethylsilyl chloride (4.6 g, 0.03 mol), and triethylamine (6 mL, 0.04 mol) in 30 mL of dry toluene was refluxed under nitrogen for 8 h. The precipitate formed was filtered and washed with a small amount of toluene. The combined toluene was distilled off, and the residue was subjected to vacuum distillation to give a colorless oil (5.0 g, 80%): bp_2 80–81 °C; IR (neat) 1585, 1295, and 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 6 H, *t*-Bu(*Me*)Si), 0.87 (s, 9 H, t-*Bu*(Me)$_2$Si), 6.63 (m, 2 H, 3- and 5-H), and 8.27 (m, 2 H, 2- and 6-H); MS, *m/e* (relative intensity, %) 209 (M^+, 17) and 152 (base peak). HRMS Calcd for $C_{11}H_{19}NOSi$: M, 209.1234. Found: *m/e* 209.1231.

General One-Pot Procedure for the Generation of 4-((*tert*-Butyldimethylsilyl)oxy)pyridinium Methylides 5–7 and the Cycloaddition Reactions with Olefinic Dipolarophiles. To a solution containing an alkylating reagent (1 mmol) in dry acetonitrile or dichloromethane (1 mL), was added slowly an equimolar amount of **1** by syringe. The mixture was stirred at room temperature under nitrogen. A dipolarophile in the same solvent (1 mmol in 1 mL) and then triethylamine (1.1–1.3 mmol) were added by syringe. The mixture was stirred at room temperature, poured into water (100 mL), and extracted with dichloromethane (20 mL × 2). The combined extracts were dried over anhydrous magnesium sulfate, evaporated *in vacuo*, and the

residue was chromatographed over silica gel using a mixture of ethyl acetate and hexane to give the desilylated cycloadduct. The reaction conditions and the results are summarized in Table I.

Spectral Data of the Desilylated Cycloadducts. All desilylated cycloadducts gave satisfactory NMR, IR, and mass spectral data as well as elemental analyses. Detailed spectral data on some representative products (**8**, **11**, **15**, **18**, and **19**) are presented in this Experimental Section. The reader is referred to the supplementary material available which contains full spectroscopic data on all other desilylated cycloadducts.

8: colorless prisms (benzene–hexane); IR (KBr) 1780, 1700, 1640, and 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (t, 1 H, J = 11.0 Hz, 9-H (endo)), 2.73 (ddd, 1 H, J = 11.0, 5.0, and 1.0 Hz, 9-H (exo)), 3.07 (s, 3 H, NMe), 3.44 (t, 1 H, J = 8.4 Hz, 9b-H), 3.67 (dd, 1 H, J = 8.4 and 1.5 Hz, 3a-H), 4.42 (ddd, 1 H, J = 11.0, 8.4, and 5.0 Hz, 9a-H), 5.17 (dd, 1 H, J = 7.5 and 1.0 Hz, 7-H), 5.61 (d, 1 H, J = 1.5 Hz, 4-H), 7.00 (d, 1 H, J = 7.5 Hz, 6-H), 7.30–7.80 (m, 3 H, Ph), and 8.10–8.30 (m, 2 H, Ph); ^{13}C NMR ($CDCl_3$) δ 25.48 (q, NMe), 39.51 (t, 9-C), 46.97, 49.08 (each d, 3a- and 9b-C), 60.47 (d, 9a-C), 67.81 (d, 4-C), 102.04 (d, 7-C), 129.05, 129.22, 132.51 (each d), 134.68 (s), 150.53 (d, 6-C), 174.02, 176.71 (each s, 1- and 3-C), 191.87 (s, COPh), and 194.56 (s, 8-C); MS, m/e (relative intensity, %) 324 (M^+, 11), 219 (57), and 134 (base peak). Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.76; H, 5.23; N, 8.38.

11: colorless prisms (ether); IR (KBr) 1750, 1720, 1690, and 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (dd, 1 H, J = 16.0 and 15.0 Hz, 8-H (endo)), 2.78 (dd, 1 H, J = 16.0 and 6.0 Hz, 8-H (exo)), 3.37 (dd, 1 H, J = 9.8 and 7.8 Hz, 1-H), 3.73 (dd, 1 H, J = 7.8 and 5.0 Hz, 2-H), 3.71, 3.77 (each s, each 3 H, COOMe), 4.22 (ddd, 1 H, J = 15.0, 9.8, and 6.0 Hz, 8a-H), 5.09 (d, 1 H, J = 7.8 Hz, 6-H), 5.64 (d, 1 H, J = 5.0 Hz, 3-H), 7.00 (d, 1 H, J = 7.8 Hz, 5-H), 7.37–7.77 (m. 3 H, Ph), and 7.83–8.10 (m, 2 H, Ph); MS, m/e (relative intensity, %) 357 (M^+, 19) and 252 (base peak). Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.84; H, 5.36; N, 3.92. Found: C, 63.74; H, 5.33; N, 3.96.

15: colorless viscous oil; IR (neat) 2225, 1740, 1640, and 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (ddd, 1 H, J = 13.9, 8.0, and 7.5 Hz, 2-H (exo)), 2.67 (dd, 1 H, J = 14.2 and 6.0 Hz, 8-H (exo)), 2.68 (t, 1 H, J = 14.2 Hz, 8-H (endo)), 2.85 (ddd, 1 H, J = 13.9, 8.8, and 2.3 Hz, 2-H (endo)), 3.45 (ddd, 1 H, J = 8.0, 6.0, and 2.3 Hz, 1-H), 3.79 (s, 3 H, COOMe), 4.13 (dt, 1 H, J = 14.2, 6.0, and 6.0 Hz, 8a-H), 4.52 (dd, 1 H, J = 8.8 and 7.5 Hz, 3-H), 5.10 (d, 1 H, J = 8.0 Hz, 6-H), and 7.16 (d, 1 H, J = 8.0 Hz, 5-H); MS, m/e (relative intensity, %) 220 (M^+, 12) and 161 (base peak). HRMS Calcd for $C_{11}H_{12}N_2O_3$: M, 220.0859. Found: m/e 220.0849.

18: colorless prisms (ethyl acetate); IR (KBr) 1690, 1640, 1570, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70–2.90 (m, 4 H, 2- and 8-H), 2.90–4.45 (m, 2 H, 1- and 8a-H), 5.09 (d, 1 H, J = 7.4 Hz, 6-H), 5.52 (t, 1 H, J = 8.0 Hz, 3-H), 7.00 (d, 1 H, J = 7.4 Hz, 5-H), and 7.30–8.00 (m, 10 H, Ph); MS, m/e (relative intensity, %) 381 (M^+, 4) and 134 (base peak). HRMS Calcd for $C_{21}H_{19}NO_4S$: M, 381.1059. Found: m/e 381.1047.

19: colorless prisms (ethyl acetate); IR (KBr) 1690, 1640, 1570, and 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92–2.39 (m, 2 H, 8-H), 2.39–3.27 (m, 2 H, 2-H), 3.45–3.90 (m, 1 H, 1-H), 4.08–4.47 (m, 1 H, 8a-H), 5.10 (d, 1 H, J = 7.4 Hz, 6-H), 5.24 (dd, 1 H, J = 9.5 and 2.0 Hz, 3-H), 6.98 (d, 1 H, J = 7.4 Hz, 5-H), and 7.35–8.00 (m, 10 H, Ph); MS, m/e (relative intensity, %) 381 (M^+, 6) and 134 (base peak). Anal. Calcd for $C_{21}H_{19}NO_4S$: C, 66.14; H, 4.99; N, 3.67. Found: C, 66.35; H, 5.03; N, 3.72.

Reaction of 5 with Dimethyl Acetylenedicarboxylate Leading to 20 and Dehydrogenation of 20 into 21. To a solution of phenacyl bromide (199 mg, 1 mmol) in dry dichloromethane (2 mL) was added slowly **1** (209 mg, 1 mmol) by syringe. The mixture was stirred at room temperature under nitrogen. Equimolar amounts of dimethyl acetylenedicarboxylate (142 mg) and triethylamine (0.14 mL) were added at −78 °C by syringe, the mixture was stirred at −78 °C for 1 h and then at room temperature for 1 day, and finally poured into water (50 mL). The dichloromethane was separated and the aqueous layer was extracted with chloroform (20 mL × 2). The combined organic layers were dried over magnesium sulfate and evaporated *in vacuo*. The residue was chromatographed through a short column packed with silica gel using ethyl acetate–chloroform (1:3) to give 142 mg (40%) of **20** as a mixture of two stereoisomers (1:1) which could not be separated by column chromatography. **20**: yellow viscous oil; IR (neat) 1740, 1700, and 1620 cm^{-1}; ^1H NMR ($CdCl_3$) δ 2.37–2.86 (m, 2 H, 8-H), 3.47, 3.81 (each s, each 3 H, COOMe), 3.96, 4.23 (each d, 1 H, J = 10.0 Hz, 1-H), 4.20–4.80 (m, 1 H, 8a-H), 5.24, 5.28 (each d, 1 H, J = 7.8 Hz, 5-H), 7.00, 7.03 (each d, 1 H, J = 7.8 Hz, 6-H), and 7.30–8.20 (m, 5 H, Ph); MS, m/e (relative intensity, %) 355 (M^+, 6), 105 (base peak), and 77 (61). HRMS Calcd for $C_{19}H_{17}NO_6$: M, 355.1053. Found: m/e 355.1053.

When **20** was left in a long column packed with silica gel and eluted with benzene after 20 h, a quantitative amount of **21** was obtained. **21**: pale yellow prisms (chloroform–ether); mp 265–267 °C; IR (KBr) 1750, 1690, and 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.27, 3.83 (each s, each 3 H, COOMe), 6.77 (dd, 1 H, J = 7.7 and 2.8 Hz, 6-H), 7.30–7.70 (m, 6 H, Ph and OH), 7.86 (dd, 1 H, J = 2.8 and 1.0 Hz, 8-H), and 9.54 (dd, 1 H, J = 7.7 and 1.0 Hz, 5-H); MS, m/e 353 (M^+, base peak). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.58; H, 4.28; N, 3.96. Found: C, 64.60; H, 4.30; N, 4.15.

Registry No. **1** (trimethylsilane deriv), 27248-04-0; **2**, 101494-09-1; **3**, 101494-10-4; **4**, 101494-11-5; **5**, 101494-12-6; **6**, 101494-13-7; **7**, 101494-14-8; **8**, 101494-15-9; **9**, 101494-16-0; **10**, 101494-17-1; **11**, 101494-18-2; **12**, 101494-19-3; **13**, 101627-08-1; **14**, 101494-20-6; **15**, 101494-21-7; **16**, 101494-22-8; **17**, 101494-23-9; **18**, 101494-24-0; **19**, 101627-09-2; **20**, 101494-25-1; **21**, 101517-36-6; $MeO_2CC{\equiv}CCO_2Me$, 762-42-5; $PhCOCH_2Br$, 70-11-1; $CNCH_2Br$, 590-17-0; MeO_2CCH_2Br, 96-32-2; (*E*)-$MeO_2CCH{=}CHCO_2Me$, 624-49-7; (*E*)-*t*-$BuO_2CCH{=}CHCO_2Bu$-*t*, 7633-38-7; (*Z*)-$MeO_2CCH{=}CHCO_2Me$, 624-48-6; (*Z*)-*t*-$BuO_2CCH{=}CHCO_2Bu$-*t*, 18305-60-7; $H_2C{=}CHCN$, 107-13-1; $PhSO_2CH{=}CH_2$, 5535-48-8; $H_2C{=}CHCO_2Me$, 96-33-3; 4-pyridinone, 108-96-3; *N*-methylmaleimide, 930-88-1; *N*-phenylmaleimide, 941-69-5.

Supplementary Material Available: ^1H NMR, IR, and mass spectral data, and analytical data for compounds **9**, **10**, **12–14**, and **16**, **17** (3 pages). Ordering information is given on any current masthead page.