Biological Assays. Albino Himalayan spotted Füllingsdorf (from Hoffmann La Roche, Basel) female guinea pigs weighing from 300 to 500 g were sensitized as described by Klecak (21): on alternate days, the hapten, emulsified in a 1:1 dispersion of saline–Freund's complete adjuvant (FCA), was injected intradermally (0.1 mL) on the shaved nuchal region of the animal (in all three injections). After 15 days of rest, the elicitation was conducted by an open epicutaneous test (OET): 25 μL of ethanolic solution of hapten was deposited on the shaved flank of the animal (on a 2-cm^2 surface delimited by a standard circular stamp). Tests were read at 24 h by using the following scale: 0 = no reaction; 0.5 = slight erythema not covering the whole test area; 1 = erythema covering the whole test area; 2 = erythema plus swelling covering the whole test area. Before starting sensitization (allergy induction), irritation thresholds (primary toxicity) were determined on FCA-injected controls (same procedure as above but without hapten and same elicitation procedure). None of the concentrations used were toxic in control animals. In each experiment eight controls (FCA treated but without the hapten). Results are collected in Table I. Student's t test was used to assess the significance of the skin reaction intensities. All the results were statistically significant.

Acknowledgment. We thank the PIREN (Programme de Recherches Interdisciplinaires) for financial support (ASP).

New Type of 1,3-Molecular Rearrangement of Substituted-Vinyl Alkoxymethyl Ethers and Its Application to Synthesis of 1(or 3)-Substituted 4-Alkoxybutan-2-ones

Xue-Ping Gu, Isao Ikeda, and Mitsuo Okahara*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka, Japan 565

Received November 25, 1987

A new type of molecular rearrangment of substituted-vinyl alkoxymethyl ethers is disclosed. A 1,3-cationotropic rearrangement mechanism via relatively stable alkoxymethyl cations is postulated. The intermediacy of transient alkoxymethyl cation ion pairs is indicated by a crossover experiment. A series of 1(or 3)-substituted 4-alkoxybutan-2-ones were synthesized in good yields by aluminum chloride catalyzed rearrangement of the corresponding 2(or 1,2)-substituted 3,5-dioxahex-1-enes.

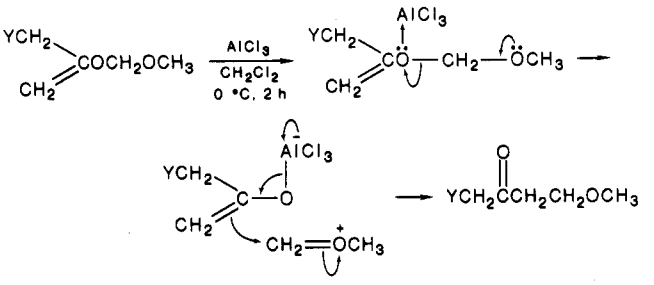
2-(Chloromethyl)-3,5-dioxahex-1-ene (**1a**) has been developed recently as an acetonylating reagent[1] which is very effective owing to the simplicity of its preparation and isolation, its stability on storage, and its high reactivity and versatility in allylation. During an investigation on the chemical reactivity of **1a** to extend its utility in organic synthesis, we found that **1a** and its derivatives undergo a new type of 1,3-migration of the methoxymethyl group in the presence of aluminum chloride to afford 1-chloro-4-methoxybutan-2-one and 1-substituted derivatives in good yields (Scheme I).

There is an extensive body of literature on molecular rearrangements such as the Claisen rearrangement which involves 3,3-sigmatropic rearrangement of vinyl allyl ethers,[2] the Fries rearrangement of phenolic esters, in which the acyl group migrates in a 1,3 manner,[3] 1,3-migration of an alkyl group by a free-radical path,[4] and so on.[5] In this paper, we disclose the results of studies on the mechanistic aspects of this new type of 1,3-molecular rearrangement of substituted-vinyl alkoxymethyl ethers and its utilization for the synthesis of a series of 1(or 3)-substituted 4-alkoxybutan-2-ones.

Results and Discussion

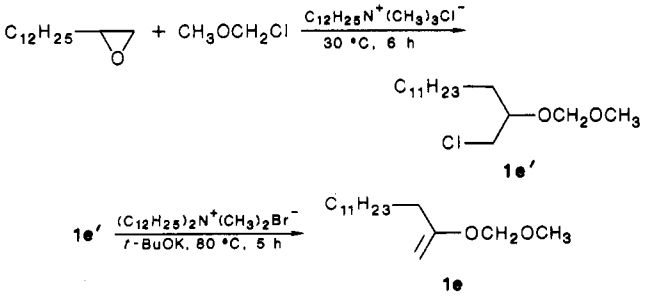
The 1,3-migration of an alkoxymethyl group in vinyl ethers **1** was first found when **1a** was treated with 1.0 equiv of aluminum chloride in dichloromethane at 0 °C for 2 h. In order to clarify the 1,3-migration mechanism, and to inspect the scope of migration reaction and the influence of the substituent, we examined several 2-substituted 3,5-dioxahex-1-enes (**1a,d–j**) and dioxaheptenes (**1b,c**). 2-Substituted 3,5-dioxahex-1-enes and dioxaheptenes

Scheme I[a]



[a] Y: Cl, RCOO, RO, RS, R_1R_2N, alkyl.

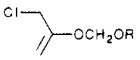
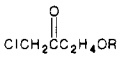
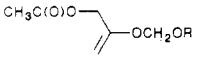
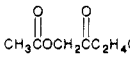
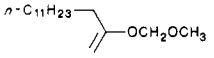
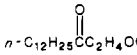
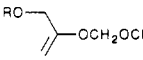
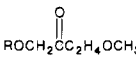
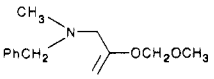
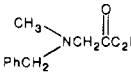
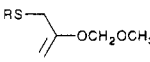
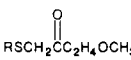
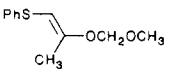
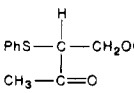
Scheme II



(1) Gu, X.-P.; Ikeda, I.; Okahara, M. *J. Org. Chem.* **1987**, *52*, 3192–3196.
(2) Bennett, G. B. *Synthesis* **1977**, 589–606.
(3) Ogata, Y.; Tabuchi, H. *Tetrahedron* **1964**, *20*, 1661–1666.
(4) Landis, P. S. *Mechanism of Molecular Migrations*; Interscience: New York, 1969; Vol. II, pp 43–63.
(5) Niederl, J. B.; Storch, E. A. *J. Am. Chem. Soc.* **1931**, *53*, 1928–1934.

0022-3263/88/1953-2737$01.50/0

Table I. 1,3-Migration of the Alkoxymethyl Group of Substituted-Vinyl Alkoxymethyl Ethers[a]

starting material			product		
	no.	R		no.	yield,[b] %
	1a 1b	CH_3 C_2H_5		2a 2b	78 86
	1c 1d	C_2H_5 CH_3		2c 2d	90 71
	1e			2e	70
	1f 1g	n-$C_{12}H_{25}$ Ph		2f 2g	75 23[c]
	1h			2h	53
	1i 1j	n-C_4H_9 Ph		2i 2j	63 40[d]
	1k			2k	81[e]

[a] $AlCl_3$, CH_2Cl_2, 0 °C for 2 h, unless otherwise stated. [b] After Kugelrohr distillation. [c] Temperature −78 °C for 24 h; acetonyl phenyl ether was also obtained as a byproduct (25%) and might be derived from unrearranged raw vinyl ether **1g** by hydrolysis.[1] [d] Temperature −78 °C for 72 h; acetonyl phenyl sulfide[1] was also obtained in 23% yield. [e] Temperature −78 °C for 24 h.

(**1a–d,f–j**) were prepared by the reaction of active proton-containing compounds with 2-(chloromethyl)-3,5-dioxahex-1-ene (**1a**) or 2-(chloromethyl)-3,5-dioxahept-1-ene in the presence of base.[1] 5-Methylene-2,4-dioxaheptadecane (**1e**) was prepared according to Scheme II. By the reaction of 1,2-epoxytetradecane with chloromethyl methyl ether in the presence of dodecyltrimethyl ammonium chloride, 1-(chloromethyl)tridecyl methoxymethyl ether (**1e′**) was obtained in 98% yield.[6] The dehydrohalogenation was subsequently carried out by treating **1e′** with potassium *tert*-butoxide under phase transfer catalytic conditions to give 5-methylene-2,4-dioxaheptadecane (**1e**) in a yield of 60%. (*E*)-1-(Phenylthio)-2-methyl-3,5-dioxahex-1-ene (**1k**) was obtained in 88% yield from 2-[(phenylthio)methyl]-3,5-dioxahex-1-ene (**1j**) through a proton migration in the presence of sodium hydroxide under phase transfer catalytic conditions.

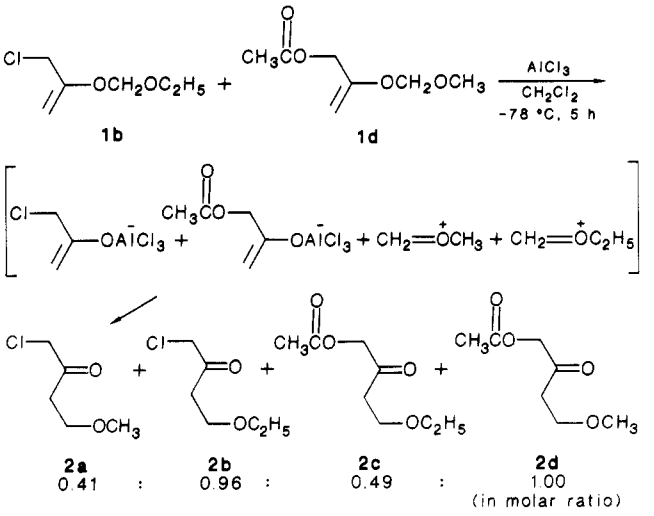
The yields of rearrangement products are usually good to excellent. The results are summarized in Table I.

Although the 1,3-molecular rearrangement proceeded regardless of the kind of substituent, it is obvious that the reactivity of vinyl ethers 1 and the yields of the rearrangement products were affected greatly by the nature of the substituent on the allyl group. Most reactions proceeded successfully at 0 °C, but in some cases (**1g**, **1j**, and **1k**), low temperature (−78 °C) was needed to avoid the formation of the polymeric substances produced at the elevated temperature. The yields of **2g** and **2j** were relatively low compared with those of the other compounds, but **2k** was obtained in high yield when the reaction was carried out at −78 °C.

The structures of compounds **2a–k** were ascertained by spectral and elemental analyses. The typical ^1H NMR spectral features of the 1-substituted 4-methoxybutan-2-ones are absorptions at δ 3.35 (s, CH_3O), 2.85 (t, J = 6.0 Hz, $OCH_2CH_2C(O)$), and 3.70 (t, J = 6.0 Hz, $OCH_2CH_2C(O)$).

The 1,3-migration mechanism of the methoxymethyl group of **1a** under the influence of aluminum chloride is

Scheme III



postulated to involve a cationotropic rearrangement via relatively stable methoxymethyl cations[7] (Scheme I). The crucial mechanistic point has been confirmed by crossover experiments.[8] Thus, a mixture of vinyl ethers **1b** and **1d** (1:1, molar ratio) was treated with a stoichiometric amount of aluminum chloride at −78 °C for 5 h to afford a mixture of **2a**, **2b**, **2c**, and **2d** in high yield in the molar ratio of 0.41:0.96:0.49:1.00 (estimated from GLC) (Scheme III). The intramolecular mechanism can be considered to be the major reaction since **2b** and **2d** were formed as the main products. However, the formation of crossover products **2a** and **2c** gives evidence of the intermolecular exchange of cationic species during the rearrangement. This also proves the existence of an intermediate (presumably a cationic species) in the mechanism. When the crossover reaction was carried out at 0 °C for 2 h, the ratio of the products changed to 0.054:1.00:0.19:0.93, repre-

(6) Gu, X.-P.; Ikeda, I.; Okahara, M. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 397.

(7) Saul, P. *The Chemistry of the Ether Linkage*; Interscience: New York, 1967; pp 111–113.

(8) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 499.

senting a lower level of formation of the crossover products **2a** and **2c**. The effect of reaction temperature on the product ratio can be attributed to the assumption that the alkoxymethyl cation ion pairs generated at the higher temperature undergo exchange faster than recombination to the rearranged product.

1(or 3)-Substituted 4-methoxybutan-2-ones, compounds **2**, were reported to be useful compounds and have been employed as a construction unit for the synthesis of pharmaceuticals.[9-12] Although there are some reports concerning the preparation of this kind of compound (for example, of 1-bromo-4-methoxybutan-2-one, 1-(phenylthio)-4-methoxybutan-2-one, etc.),[12-15] as far as we are aware, a general and effective synthetic method has not been developed. The 1,3-migration of the methoxymethyl moiety of vinyl ethers **1** to afford 1(or 3)-substituted 4-methoxybutan-2-ones in high yield has significant value in organic synthesis, because the 4-alkoxy-2-oxobutyl group ($ROC_2H_4C(O)CH_2$) can be introduced into many kinds of active proton-containing compounds.

2-(Chloromethyl)-3,5-dioxahex-1-ene (**1a**) is an interesting compound because of the multiple types of reactivity available. The presence of the allylic chloride, acetal linkage, and vinyl ether groups within the same molecule allows the possibility of substitution reactions,[1] hydrolysis to carbonyl compounds,[1] formation of π-allyl complexes,[16] and 1,3-molecular rearrangement.

Experimental Section

^{1}H NMR spectra were recorded on a JEOL-PS-100 instrument in $CDCl_3$ with Me_4Si as internal standard. Mass spectra were measured on a Hitachi RMU-6E spectrometer. Infrared spectra were obtained on a Hitachi 260-10 spectrometer. All the reagents were of reagent grade and were used without further purification. 2-(Chloromethyl)-3,5-dioxahex-1-ene (**1a**) and corresponding substituted-vinyl alkoxymethyl ethers were prepared according to ref 1. Evaporative distillation (Kugelrohr distillation) was performed from bulb to bulb by a glass tube oven Model GTO-250RS.

General Procedure for the Rearrangement Reaction of Substituted-Vinyl Alkoxymethyl Ethers. 1-Chloro-4-methoxybutan-2-one (2a). A solution of vinyl ether (**1a**,[1] 6.8 g, 50 mmol) in dichloromethane (30 mL) was added dropwise to a suspension of aluminum chloride (6.8 g, 50 mmol) in dichloromethane (60 mL) during a period of 20 min at 0 °C, and the mixture was stirred for an additional 2 h. Then, the reaction mixture was poured into 150 mL of an ice–water mixture and stirred for 10 min. Extraction with ether (150 mL × 2), drying over anhydrous magnesium sulfate, removal of solvent, and Kugelrohr distillation at reduced pressure gave 5.3 g (78%) of **2a** as a colorless liquid: bp 80 °C (30 Torr); ^{1}H NMR ($CDCl_3$) δ 2.85 (t, J = 6.0 Hz, 2 H), 3.30 (s, 3 H), 3.70 (t, J = 6.0 Hz, 2 H), 4.15 (s, 2 H); MS, m/e (relative intensity) 137 ($M^+ - 1$), 135 ($M^+ - 1$), 87 (30), 45 (100); IR (neat) 2950, 1740, 1130 cm^{-1}. Anal. Calcd for $C_5H_9ClO_2$: C, 43.97; H, 6.64; Cl, 25.96. Found: C, 43.68; H, 6.63; Cl, 26.23.

2-(Chloromethyl)-3,5-dioxahept-1-ene (1b). By using the procedure under phase transfer catalytic conditions reported in ref 1, we obtained **1b** in 74% yield (11.3 g, 0.10-mol scale) as a colorless liquid: bp 64–65 °C (30 Torr); ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 3 H), 3.55–3.90 (q, 2 H), 4.00 (s, 2 H), 4.40 (s, 2 H), 5.10 (s, 2 H); MS, m/e (relative intensity) 152 (M^+), 150 (M^+), 68 (31), 59 (100); IR (neat) 3000, 1640, 1300, 1160, 1120, 1030, 850, 750 cm^{-1}. Anal. Calcd for $C_6H_{11}ClO_2$: C, 47.85; H, 7.36; Cl, 23.54. Found: C, 47.80; H, 7.55; Cl, 23.25.

1-Chloro-4-ethoxybutan-2-one (2b). By the general procedure described above, we obtained **2b** in 86% yield (6.5 g, 50-mmol scale) as a colorless liquid: bp 80 °C (20 Torr); ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J = 7.0 Hz, 3 H), 2.83 (t, J = 6.0 Hz, 2 H), 3.35–3.95 (m, 4 H), 4.20 (s, 2 H); MS, m/e (relative intensity) 151 ($M^+ - 1$), 149 ($M^+ - 1$), 101 (28), 59 (100), 31 (60); IR (neat) 2950, 1740, 1130 cm^{-1}. Anal. Calcd for $C_6H_{11}ClO_2$: C, 47.85; H, 7.36; Cl, 23.54. Found: C, 47.48; H, 7.25; Cl, 23.42.

1-Acetoxy-4-ethoxybutan-2-one (2c). By the general procedure described above, we obtained **2c** in 90% yield (7.8 g, 50-mmol scale) as a colorless liquid: bp 110 °C (20 Torr); ^{1}H NMR ($CDCl_3$) δ 1.14 (t, J = 7.0 Hz, 3 H), 2.15 (s, 3 H), 2.64 (t, J = 6.0 Hz, 2 H), 3.30–3.80 (m, 4 H), 4.72 (s, 2 H); MS, m/e (relative intensity) 174 (M^+), 101 (33), 59 (100), 43 (77), 31 (33); IR (neat) 2900, 1740, 1380, 1240, 1120 cm^{-1}. Anal. Calcd for $C_8H_{14}O_4$: C, 55.15; H, 8.10. Found: C, 54.90; H, 7.98.

1-Acetoxy-4-methoxybutan-2-one (2d). By the general procedure described above, we obtained **2d** in 71% yield (2.3 g, 20-mmol scale) as a colorless liquid: bp 105 °C (20 Torr); ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3 H), 2.66 (t, J = 6.0 Hz, 2 H), 3.37 (s, 3 H), 3.68 (t, J = 6.0 Hz, 2 H), 4.72 (s, 2 H); MS, m/e (relative intensity) 161 ($M^+ + 1$), 100 (21), 87 (50), 45 (100), 43 (85); IR (neat) 2900, 1740, 1380, 1240, 1120, 1080 cm^{-1}. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.13; H, 7.55.

5-Methylene-2,4-dioxaheptadecane (1e). Potassium *tert*-butoxide (5.0 g, 45 mmol) and didodecyldimethylammonium bromide (0.28 g, 1.5 mmol, as a phase transfer catalyst) were added to 1-(chloromethyl)tridecyl methoxymethyl ether[6] (8.7 g, 30 mmol), and the mixture was heated to 80 °C for 5 h. Dichloromethane (50 mL) was added at room temperature, and solid material was removed by filtration through a short column filled with silica gel and washed with dichloromethane. After evaporation of the solvent, **1e** was isolated by Kugelrohr distillation at reduced pressure in 60% yield (4.7 g) as a colorless oil: bp 90 °C (0.05 Torr); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.0 Hz, 3 H), 1.10–2.25 (m, 22 H), 3.40 (s, 3 H), 4.10 (s, 2 H), 5.00 (s, 2 H); MS m/e (relative intensity 256 (M^+), 45 (100); IR (neat) 2900, 1640, 1490, 1170, 1040 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 74.73; H, 12.51.

1-Methoxypentadecan-3-one (2e). By the general procedure described above, we obtained **2e** in 70% yield (3.2 g, 18-mmol scale) as a white waxy solid: bp 85 °C (0.05 Torr); mp 29.5–30.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.0 Hz, 3 H), 1.10–1.80 (m, 20 H), 2.30–2.90 (m, 4 H), 3.30 (s, 3 H), 3.50–3.80 (t, 2 H); MS, m/e (relative intensity) 256 (M^+), 101 (76), 87 (100), 45 (63); IR (neat) 2900, 1710, 1460, 1130 cm^{-1}. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 74.64; H, 12.53.

1-(Dodecyloxy)-4-methoxybutan-2-one (2f). By the general procedure described above, we obtained **2f** in 75% yield (4.3 g, 20-mmol scale) as a colorless liquid: bp 110 °C (0.05 Torr); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 6.0 Hz, 3 H), 1.10–1.80 (m, 20 H), 2.85 (t, J = 6.0 Hz, 2 H), 3.45 (s, 3 H), 3.70 (t, J = 6.0 Hz, 2 H), 4.10 (s, 2 H); MS, m/e (relative intensity) 286 (M^+), 71 (79), 70 (91), 57 (100), 43 (74); IR (neat) 2950, 2900, 1740, 1130 cm^{-1}. Anal. Calcd for $C_{17}H_{34}O_3$: C, 71.28; H, 11.96. Found: C, 70.96; H, 11.94.

1-Phenoxy-4-methoxybutan-2-one (2g). 1-Phenoxy-2-methylene-3,5-dioxahexane (**1g**, 1.94 g, 10 mmol) was treated with aluminum chloride (1.3 g, 10 mmol) at −78 °C for 24 h. With the usual workup, **2g** was isolated by Kugelrohr distillation at reduced pressure in 23% yield (0.45 g) as a colorless liquid: bp 80 °C (0.3 Torr); ^{1}H NMR ($CDCl_3$) δ 2.80 (t, J = 6.0 Hz, 2 H), 3.40 (s, 3 H), 3.70 (t, J = 6.0 Hz, 2 H), 4.62 (s, 2 H), 6.75–7.50 (m, 5 H); MS, m/e (relative intensity) 194 (M^+), 107 (50), 77 (70), 45 (100); IR (neat) 2900, 1740, 1600, 1500, 1240, 1120, 760, 700 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.90; H, 7.11.

1-(*N*-Benzyl-*N*-methylamino)-4-methoxybutan-2-one (2h). By the general procedure described above, we obtained **2h** in 53% yield (2.3 g, 20-mmol scale) as a colorless liquid: bp 90 °C (0.05 Torr); ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.65 (t, J = 6.0 Hz, 2 H), 3.14 (s, 2 H), 3.45–3.75 (m, 4 H), 7.34 (s, 5 H); MS, m/e (relative intensity) 221 (M^+), 134 (90), 91 (100); IR (neat) 2950, 1730, 1460,

(9) Stoeck, V.; Schunack, W. *Arch. Pharm.* **1975**, *308*, 892–894.
(10) Weller, D. D.; Stirchak, E. P.; Weller, D. L. *J. Org. Chem.* **1983**, *48*, 4597–4605.
(11) Adachi, I.; Yamamori, T.; Ueda, M.; Doteuchi, M. Ger. Offen. DE 3432985, 1985.
(12) Humberto, C.; Jack, A. et al. *Can. J. Chem.* **1982**, *60*, 2295–2312.
(13) Yoneda, N.; Kiuchi, T.; Fukuhara, T.; Suzuki, A. *Chem. Lett.* **1984**, 1617–1618.
(14) Bates, D. K.; Jones, M. C. *J. Org. Chem.* **1978**, *43*, 3856–3861.
(15) Thyagarajan, B. S.; Majumdar, K. C.; Bates, D. K. *J. Heterocycl. Chem.* **1975**, *12*, 59–66.
(16) Gu, X.-P.; Okuhara, T.; Ikeda, I.; Okahara, M. *Synthesis*, in press.

1390, 1130, 760, 720 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.32. Found: C, 70.36; H, 8.62; N, 6.48.

1-(Butylthio)-4-methoxybutan-2-one (2i). By the general procedure described above, we obtained **2i** in 63% yield (1.2 g, 10-mmol scale) as a colorless liquid: bp 75 °C (0.2 Torr); ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 6.0 Hz, 3 H), 1.10–1.72 (m, 4 H), 2.45 (t, J = 6.0 Hz, 2 H), 2.85 (t, J = 6.0 Hz, 2 H), 3.30 (s, 3 H), 3.60–3.90 (m, 4 H); MS, m/e (relative intensity) 190 (M^+), 102 (38), 87 (44), 61 (75), 45 (100); IR (neat) 2950, 1720, 1140 cm^{-1}. Anal. Calcd for $C_9H_{18}O_2S$: C, 56.80; H, 9.53; S, 16.85. Found: C, 56.54; H, 9.51; S, 16.82.

1-(Phenylthio)-4-methoxybutan-2-one (2j). 1-(Phenylthio)-2-methylene-3,5-dioxahexane (**1j**, 4.2 g, 20 mmol) was treated with aluminum chloride (2.6 g, 20 mmol) in dichloromethane at −78 °C for 3 days. With the usual workup, **2j** was obtained in 40% yield (1.7 g) as a colorless liquid: bp 90 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 2.82 (t, J = 6.0 Hz, 2 H), 3.30 (s, 3 H), 3.45–3.80 (m, 4 H), 7.30 (s, 5 H); MS, m/e (relative intensity) 210 (M^+), 123 (100), 77 (37), 45 (79); IR (neat) 2900, 1710, 1120, 760, 700 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.22. Found: C, 62.61; H, 6.54; S, 15.03.

(*E*)-1-(Phenylthio)-2-methyl-3,5-dioxahex-1-ene (1k). A mixture of 2-[(phenylthio)methyl]-3,5-dioxahex-1-ene (**1j**, 2.1 g, 10 mmol), sodium hydroxide (pellet, 0.4 g, 10 mmol), and tetrabutylammonium bisulfate (0.17 g, 0.5 mmol) in dioxane (10 mL) was stirred at 90 °C for 1 h. The solid material was removed by filtration through a short column filled with silica gel. After evaporation of the solvent, **1k** was obtained by Kugelrohr distillation at reduced pressure in 88% yield (1.9 g) as a colorless liquid: bp 90 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 3.45 (s, 3 H), 5.08 (s, 2 H), 5.48 (s, 1 H), 7.24 (s, 5 H); MS, m/e (relative intensity) 210 (M^+), 135 (80), 45 (100); IR (neat) 2900, 1620, 1580, 1150, 1040, 730 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.22. Found: C, 62.49; H, 6.71; S, 15.01.

The hydrolysis of **1k** in 1% aqueous sulfuric acid also gave acetonyl phenyl sulfide.[1]

3-(Phenylthio)-4-methoxybutan-2-one (2k). By the same procedure used for **2g**, we obtained **2k** in 81% yield (3.4 g, 20-mmol scale) as a slightly greenish liquid: bp 90 °C (0.05 Torr); ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 3.36 (s, 3 H), 3.6–4.0 (m, 3 H), 7.30–7.60 (m, 5 H); MS, m/e (relative intensity) 210 (M^+), 178 (30), 135 (100), 91 (53), 43 (23); IR (neat) 2900, 1710, 1110, 740, 700 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.22. Found: C, 62.58; H, 6.66; S, 15.40.

Registry No. **1a**, 105104-40-3; **1b**, 114250-45-2; **1c**, 114250-46-3; **1d**, 114250-47-4; **1e**, 114250-48-5; **1f**, 114273-20-0; **1g**, 105104-43-6; **1h**, 114250-49-6; **1i**, 114250-50-9; **1j**, 114250-51-0; **1k**, 114250-52-1; **2a**, 87308-03-0; **2b**, 57429-13-7; **2c**, 114250-53-2; **2d**, 114250-54-3; **2e**, 114250-55-4; **2f**, 114250-56-5; **2g**, 114250-57-6; **2h**, 114250-58-7; **2i**, 114250-59-8; **2j**, 35737-56-5; **2k**, 114250-60-1; (chloromethyl)tridecyl methoxymethyl ether, 114250-61-2.

Metalation/$S_{RN}1$ Coupling in Heterocyclic Synthesis. A Convenient Methodology for Ring Functionalization

L. Estel, F. Marsais, and G. Quéguiner*

Laboratoire de chimie organique fine et hétérocyclique (LCOFH), l'IRCOF, INSA de Rouen, BP 08, 76131 Mont Saint Aignan, France

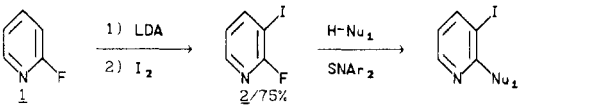
Received August 10, 1987

Lithiation, iodination, and fluorine substitution on 2-fluoropyridine gave 2-substituted 3-iodopyridines, which were further subjected to iodine $S_{RN}1$ substitution by carbon, sulfur, and phosphorus nucleophiles. Iodine substitution by enolates on 2-amino-3-iodopyridines afforded ketones, which were further cyclized to various 1,2-disubstituted pyrrolo[2,3-*b*]pyridines. 2-Amino-3-iodo-, 3-amino-4-iodo-, and 4-amino-3-iodopyridines were prepared by directed metalation of 2-, 3-, and 4-(pivaloylamino)pyridines. Substitution of iodine by enolates under $S_{RN}1$ conditions and acidic cyclization led to various 2-substituted pyrrolo[2,3-*b*]-, -[2,3-*c*]-, and -[3,2-*c*]pyridines in high yields.

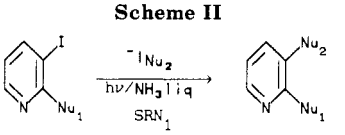
Introduction

In connection with synthetic efforts, chemists require more and more specific functionalization methods for π-deficient heterocycles (pyridine, quinoline, ...). Much has been done in this area with the recent developments of such powerful reactions as the directed ortho lithiation,[1] the $S_{RN}1$ substitution,[2] or the transition metal catalyzed cross coupling reaction.[3] The two last strategies are important synthetic methods that require prior access to substituted derivatives such as aryl halides. This constitutes an important drawback in the π-deficient heterocyclic series, where an increase in the degree of substitution is often difficult to carry out with suitable regio- and chemoselectivity. An answer to this problem can be given by the combination of two complementary reactions such as metalation and $S_{RN}1$ substitution. This strategy was successful with simple halo- or aminopyridines, and the results of the study are reported in this paper.

Scheme I



Scheme II



Nu_1	:	F	OMe	NH_2	NHMe	OMe	OMe
Nu_2	:		$-ICH_2-CO-tBu$			$-IPO(OEt)_2$	$-IS-CH_2-CH_2-OH$
Compd.	:	6	7	8	9	10	11
Yield	:	92%	84%	87%	50%	78%	80%

(1) For a comprehensive review on directed ortho lithiation, see: Gschwend, H. W.; Roriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. For a recent review on π-deficient heterocycle metalation, see: Marsais, F.; Quéguiner, G. *Tetrahedron* **1983**, *39*, 2009.

(2) Beugelmans, R.; Boudet, B.; Quintero, L. *Tetrahedron Lett.* **1980**, *21*, 1943. Bard, R. R.; Bunnett, J. F. *J. Org. Chem.* **1980**, *45*, 1546.

(3) Dieck, H. A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 1133. Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947.

0022-3263/88/1953-2740$01.50/0