Published in Synthesis 5, 381-383, 1988
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# Synthesis of Pyrroles via the Cross-Aldol Reaction

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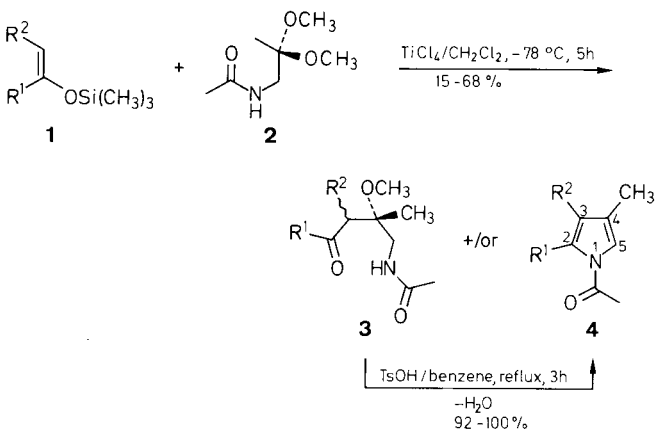
Substituted pyrroles and pyrrolo[1,2-*b*]isoquinoline derivatives are obtained via the cross-aldol reaction of silyl enol ethers with *N*-acylaminoacetone acetals or phthalimidoacetone acetals, respectively.

The synthesis of pyrroles gains its importance from the fact that these heterocycles are the dominant subunits in the pigments of life.[1] The pyrrole synthesis most often used today is the Knorr reaction.[2] In this intermolecular cyclocondensation, the N–C bond is formed first, followed by the formation of the C–C bond.[3] In contrast to the Knorr reaction, the biosynthesis proposed for porphobilinogen seems to have an inverted sequence: C–C bond formation first, followed by N–C bond formation.[4] The Knorr synthesis is most satisfactory when the second component is a β-oxoester or a β-diketone, which can provide additional stabilization to the intermediate enamine. Usually, simple carbonyl compounds cannot be used successfully[2] so that *C*-alkylpyrroles have to be synthesized via transformation of methoxycarbonyl- or acylpyrroles prepared by the Knorr reaction.[5]

We report here a synthesis of *N*-acyl-*C*-alkylpyrroles starting from silyl enol ethers **1a–d** and the *N*-acylaminoacetone acetal **2** or the phthalimidoacetone acetal **5** (Schemes **A** and **B**). Since *N*-acetyl groups on pyrroles can be easily removed[6] by hydrolysis, the reported procedure can also be used for the synthesis of *N*-unsubstituted pyrroles. The synthesis proceeds via initial C–C bond formation and thus mimics closely the proposals for the biosynthesis of porphobilinogen.[4] The formation of the pyrrole proceeds via a $TiCl_4$-catalyzed aldol reaction[7] followed by condensation and elimination of methanol (either as a one-pot or a two-pot reaction). Modifying the original conditions,[7] we found that adding a large excess of titanium(IV) chloride (4–6 equivalents) to a solution of the acetal **2** in dichloromethane at −78 °C, immediately followed by the addition of a solution of the silyl enol ether **1** affords reasonable to good yields of the aldol products **3** or, in some cases, of the alkylpyrroles **4** (Tables 1, 2, 3). From a mixture of the silyl enol ethers **1a** and **1b** in the ratio 3:1[8] and acetal **2**, the pyrroles **4a** (38%) and **4b** (5%) were obtained directly and the aldol product **3b** was isolated in 12% yield; product **3b** could be smoothly transformed into the pyrrole **4b** (92%) to give a total yield of **4b** of 16%. From the cyclic silyl enol ether **1d**, a pyrrole could not be obtained under




| 1, 3, 4 | $R^1$ | $R^2$ | 1, 3, 4 | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **a** | $CH_3$ | $CH_2CO_2CH_3$ | **c** | | $-(CH_2)_3CO-$ |
| **b** | $(CH_2)_2CO_2CH_3$ | H | **d** | | $-(CH_2)_3-$ |

Scheme **A**

**Table 1.** Reaction of Silyl Enol Ethers **1** with *N*-Substituted Aminoacetone Acetals **2** or **5**

| Silyl Enol Ether | Acetal | Aldol Product | Yield[a] (%) | Molecular Formula | MS *m/z* (%) | Pyrrole Derivative | Yield[a] based on **1** | mp (°C) | Molecular Formula | MS *m/z* (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** + **1b** (3:1) | **2** | | | | | **4a** | 38 | oil | $C_{11}H_{15}NO_3$[b] (209.2) | 209 ($M^+$, 93); 167 (84); 108 (100) |
| | | +**3b** | 12 | $C_{12}H_{21}NO_5$ (259.3) | 260[f] ($M^+ + 1$, 30); 115 (100) | **4b** | 16[c] | oil | $C_{11}H_{15}NO_3$ (209.2) | 209 ($M^+$, 63); 167 (96); 108 (85); 94 (100) |
| **1c** | **2** | | | | | **4c** | 15 | 89–93 (hexane) | $C_{11}H_{13}NO_2$[b] (191.2) | 191 ($M^+$, 57); 149 (80); 121 (100) |
| **1d** | **2** | **3d** | 83 | $C_{11}H_{19}NO_3$ (213.3) | 214[f] ($M^+ + 1$, 1); 141 (100) | **4d** | 68 | 55–60[d] | $C_{10}H_{13}NO$[b] (163.2) | 163 ($M^+$, 81); 121 (100); 120 (100) |
| **1a** + **1b** (3:1) | **5** | **6a** | 65 | $C_{18}H_{21}NO_6$ (347.4) | 348[f] ($M^+ + 1$, 2); 187 (100) | **7a** | 20 | 217–219 (EtOH) | $C_{17}H_{15}NO_4$[b] (297.3) | 297 ($M^+$, 44); 238 (100) |
| | | +**6b** | 20 | $C_{18}H_{21}NO_6$ (347.4) | | **7b** | 7 | 131–141[e] (EtOH) | $C_{17}H_{15}NO_4$[b] (297.3) | 297 (47); 238 (74); 237 (100) |

[a] Yield of isolated product.
[b] Satisfactory microanalyses obtained: C ±0.18, H ±0.12, N ±0.34.
[c] Yield of direct conversion **1** → **4b** (4%) + yield of the two-step sequence **1** → **3b** → **4b** (11%), the latter yield being calculated from 12% yield in the first step and 92% yield in the second step (i.e., 12% of 92%).
[d] Analytical data obtained from the distilled product: bp 60–70 °C (Kugelrohr oven)/0.02 Torr.
[e] In spite of three recrystallizations, the melting range remained unusually wide.
[f] The protonated form is observed instead of the molecular peak.[13]

the same conditions, but the aldol product **3d** was isolated in 83% yield; acid-catalyzed intramolecular cyclocondensation of **3d** afforded the pyrrole **4d** in 68% yield. Using a deactivated silyl enol ether such as **1c** lowered the yield considerably and only 15% of **4c** were obtained; no aldol product detected in the reaction mixture.

By using the *N*-phthaloylaminoacetone acetal **5** in place of the *N*-acetyl derivative **2**, the yields of the aldol reaction were considerably increased; thus products **6a** and **6b** (the analogs of **3a, b**) were obtained in 87 and 80% yields, respectively (Scheme **B**). Unfortunatly, the hydrolysis of **6a** and **6b** proved to be difficult. Treatment of **6a** and **6b** with concentrated hydrochloric acid in methanol afforded the ring-fused pyrrole derivatives **7a** and **7b** in moderate yields via an intramolecular Friedel-Crafts reaction of a hydrolysis intermediate.

In summary, the procedure described here affords substituted pyrroles from easily available starting materials and it complements the classical Knorr procedure. Yields are low when the silyl enol ether is deactivated.

**Table 2.** Spectral Data of Compounds **3** and **6**

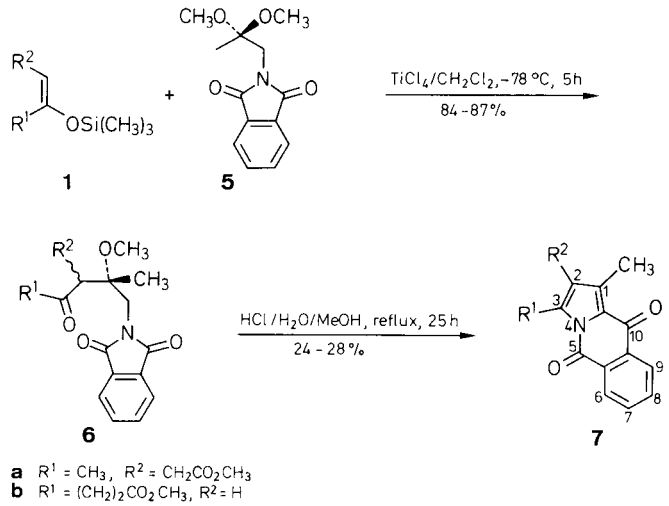
| Compound | IR $\nu$ (cm$^{-1}$) | $^1$H-NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}$C-NMR ($CDCl_3$/TMS) $\delta$ |
|---|---|---|---|
| **3b** | 2850, 1745, 1710, 1660[a] | 1.26 (s, 3H, $CCH_3$); 2.00 (s, 3H, $COCH_3$); 2.57 (m, 2H, $CH_2CO_2$); 2.61 (d, 1H, $J$ = 14.6, COCHHC); 2.67 (d, 1H, $J$ = 14.6, COCHHC); 2.78 (m, 2H, $CH_2CO$); 3.24 (s, 3H, $OCH_3$); 3.28 (dd, 1H, $J$ = 14, 5.4, CCHHN); 3.49 (dd, 1H, $J$ = 14, 6.6; CCHHN); 3.68 (s, 3H, $CO_2CH_3$); 6.01 (br s, 1H, NH) | 20.8 (q); 23.2 (q); 27.7 (t); 39.2 (t); 44.9 (t); 48.7 (t); 49.5 (q); 51.7 (q); 75.9 (s); 170.3 (s); 173.2 (s); 207.4 (s) |
| **3d**[b] | 2840, 1735, 1660[a] | 1.12 (s, 3H, $CCH_3$); 1.98 (s, 3H, $CH_3CON$); 2.5–1.6 (m, 7H, $CHCH_2CH_2CH_2$); 3.22 (s, 3H, $OCH_3$); 3.52 (dd, 1H, $J$ = 5.8, 13.5, CCHHN); 3.58 (dd, 1H, $J$ = 5.6, 13.5, CCHHN); 5.92 (br s, 1H, NH) | 18.3 (q); 20.3 (t); 23.2 (q); 25.5 (t); 40.1 (t); 43.7 (t); 49.5 (q); 53.1 (d); 77.3 (s); 170.2 (s); 217.6 (s) |
| | | 1.24 (s, 3H, $CCH_3$); 2.00 (s, 3H, $CH_3CON$); 2.5–1.6 (m, 7H, $CHCH_2CH_2CH_2$); 3.19 (s, 3H, $OCH_3$); 3.37 (dd, 1H, $J$ = 5.1, 13.9, CCHHN); 3.49 (dd, 1H, $J$ = 6.3, 13.9, CCHHN); 6.48 (br s, 1H, NH) | 16.0 (q); 19.8 (t); 22.4 (q); 25.8 (q); 40.2 (t); 44.0 (t); 49.8 (q); 54.5 (d); 77.2 (s)[c] |
| **6a**[b] | 2840, 1770, 1725, 1710[d] | 1.22 (s, 3H, $CCH_3$); 2.25 (s, 3H, $CH_3CO$); 2.86 (dd, 1H, $J$ = 4.4, 17.0, $CHHCO_2$); 2.92 (dd, 1H, $J$ = 9.8, 17.0, $CHHCO_2$); 3.23 (dd, 1H, $J$ = 4.4, 9.8, CH); 3.26 (s, 3H, $OCH_3$); 3.54 (d, 1H, $J$ = 14.8, CCHHN); 3.67 (s, 3H, $CH_3O_2C$); 3.85 (dd, 1H, $J$ = 14.8, CCHHN); 7.73 (m, 2H$_{arom}$); 7.85 (m, 2H$_{arom}$) | 16.3 (q); 33.1 (t); 34.0 (q); 41.3 (t); 50.0 (q); 51.1 (d); 51.8 (q); 78.6 (s); 123.5 (d); 131.9 (s); 134.0 (d); 168.5 (s); 172.9 (s); 211.0 (s) |
| | | 1.24 (s, 3H, $CCH_3$); 2.35 (s, 3H, $CH_3CO$); 2.65 (dd, 1H, $J$ = 3.3, 17.0, $CHHCO_2$); 3.0 (dd, 1H, $J$ = 10.9, 17.0, $CHHCO_2$); 3.31 (s, 3H, $OCH_3$); 3.37 (dd, 1H, $J$ = 3.3, 10.9, CH); 3.67 (d, 1H, $J$ = 14.3, CCHHN); 3.67 (s, 3H, $CH_3O_2C$); 3.85 (d, 1H, $J$ = 14.3, CCHHN); 7.73 (m, 2H$_{arom}$); 7.85 (m, 2H$_{arom}$) | |
| **6b** | | 1.37 (s, 3H, $CCH_3$); 2.59 (d, 1H, $J$ = 15.5, COCHHC); 2.70 (m, 4H, $CH_2CH_2$); 2.71 (d, 1H, $J$ = 15.5, COCHHC); 3.31 (s, 3H, $OCH_3$); 3.67 (s, 3H, $CH_3O_2C$); 3.79 (d, 1H, $J$ = 14.2, CCHHN); 3.89 (d, 1H, $J$ = 14.2, CCHHN); 7.72 (m, 2H$_{arom}$); 7.84 (m, 2H$_{arom}$) | |

[a] Film.
[b] Two diastereoisomers, not separated.
[c] For the carbonyl C-atoms, only one set of signals was observed.
[d] KBr.

**Table 3.** Spectral Data of Compounds **4** and **7**

| Compound | IR $\nu$ (cm$^{-1}$) | UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) | $^1$H-NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}$C-NMR ($CDCl_3$/TMS) $\delta$ |
|---|---|---|---|---|
| **4a** | 1740, 1715[a] | | 1.99 (d, 3H, $J$ = 1.2, 4-$CH_3$); 2.43 (s, 3H, 2-$CH_3$); 2.47 (s, 3H, $CH_3CO$); 3.37 (s, 2H, 3-$CH_2$); 3.68 (s, 3H, $OCH_3$); 6.79 (m, 1H, H-5) | 10.0 (q); 13.1 (q); 23.8 (q); 29.5 (t); 51.6 (q); 116.5 (d); 117.8 (s); 121.8 (s); 129.7 (s); 168.6 (s); 171.5 (s) |
| **4b** | 1735, 1720[a] | | 2.01 (d, 3H, $J$ = 1.2, 4-$CH_3$); 2.48 (s, 3H, $CH_3CO$); 2.63 (m, 2H, 2-$CH_2$); 3.18 (m, 2H, $CH_2CO$); 3.66 (s, 3H, $OCH_3$); 5.87 (m, 1H, H-3); 6.75 (m, 1H, H-5) | 11.7 (q); 24.1 (q); 24.8 (t); 33.5 (t); 51.5 (q); 114.8 (d); 117.8 (d); 122.1 (s); 135.3 (s); 168.8 (s); 173.4 (s) |
| **4c** | 1725, 1665[b] | | 2.12 (m, 2H, $CH_2CH_2CH_2$); 2.26 (d, 3H, $J$ = 1.3, 4-$CH_3$); 2.46 (m, 2H, $CH_2CH_2CO$); 2.52 (s, 3H, $CH_3CON$); 3.19 (m, 2H, 2-$CH_2$); 6.75 (m, 1H, H-5) | 11.6 (q); 23.5 (t); 24.2 (q); 25.3 (t); 38.4 (t); 118.1 (d); 122.0 (s); 122.9 (s); 145.9 (s); 169.2 (s); 196.3 (s) |
| **4d** | 1710[c] | | 1.99 (d, 3H, $J$ = 1.2, 4-$CH_3$); 2.40 (s, 3H, $CH_3CON$); 2.40 (m, 2H, $CH_2CH_2CH_2$); 2.50 (m, 2H, 3-$CH_2CH_2$); 2.91 (m, 2H, 2-$CH_2CH_2$); 6.88 (br s, 1H, H-5) | 10.8 (q); 22.6 (q); 23.9 (t); 28.4 (t); 28.6 (t); 119.2 (d); 119.6 (s); 128.3 (s); 133.0 (s); 167.3 (s) |
| **7a** | 1730, 1705[c] | 233 (5.03), 266 (4.94), 320 (4.45), 388 (4.32) | 2.52 (s, 3H, 1-$CH_3$); 2.65 (s, 3H, 3-$CH_3$); 3.48 (s, 2H, 2-$CH_2$); 3.71 (s, 3H, $OCH_3$); 7.75 (m, 2H, H-6 and H-9); 8.23 (m, 1H, H-7 or H-8); 8.30 (m, 1H, H-7 or H-8) | 11.2 (q); 13.9 (q); 29.2 (t); 52.2 (q); 121.1 (s); 126.3 (d); 128.9 (d); 129.9 (s); 133.0 (d); 134.1 (d); 134.5 (s); 136.3 (s); 136.7 (s); 159.8 (s); 170.9 (s); 173.6 (s) |
| **7b** | 1745, 1700[c] | 232 (5.13), 267 (5.02), 319 (4.48), 376 (4.43) | 2.53 (s, 3H, 1-$CH_3$); 2.77 (m, 2H, 3-$CH_2$); 3.41 (m, 2H, $CH_2CO$); 3.67 (s, 3H, $CH_2CO_2$); 6.14 (s, 1H, H-2); 7.76 (m, 2H, H-6 and H-9); 7.83 (m, 1H, H-7 or H-8); 8.30 (m, 1H, H-7 or H-8) | 13.5 (q); 25.0 (t); 32.3 (t); 51.7 (q); 117.7 (d); 126.6 (d); 127.2 (s); 128.9 (d); 129.9 (s); 133.0 (d); 134.1 (d); 134.4 (s); 136.7 (s); 140.7 (s); 159.6 (s); 172.8 (s); 173.6 (s) |

[a] Film. [b] In $CHCl_3$. [c] KBr.




**a** $R^1 = CH_3$, $R^2 = CH_2CO_2CH_3$
**b** $R^1 = (CH_2)_2CO_2CH_3$, $R^2 = H$

Scheme **B**

The silyl enol ethers **1a**,[8] **1b**,[8] **1c**,[9] and **1d**,[10] were obtained by literature procedures. Titanium(IV) chloride (Fluka Chemical Co., purum) was distilled from copper powder (Siegfried purum) and stored under $N_2$. Dichloromethane was distilled from $CaH_2$ under $N_2$ prior to use. Reagent quality solvents purchased from Fluka Chemical Co. or Merck were used without further purification. Molecular sieves (Typ 3A 1/8" pellets) were purchased from Union Carbide. Silica gel 60 (230–400 Mesh ASTM) and analytical TLC plates (silica gel 60 $F_{254}$) were purchased from Merck. Melting points were taken using a Kofler hot-stage melting point apparatus (Reichert Thermovar). Microanalyses were performed with a Perkin-Elmer 240 CHN-Analyser. Mass spectra were obtained using a Vacuum Generators Micromass 7070 E spectrometer. IR spectra were recorded on a Perkin-Elmer 599 spectrophotometer, UV spectra on a Perkin-Elmer 320 spectrophotometer. $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Bruker AM 360/52 spectrometer with TMS as internal standard.

The acetals are prepared conventionally[11] by refluxing the ketones[12,13] (20 mmol) in MeOH (20 mL) with trimethyl orthoformate (6.6 mL, 60 mmol) and a catalytic amount of *p*-toluenesulfonic acid (5–10 mol %) for 12 h. The solution is neutralized with $Na_2CO_3$ and filtered through celite. The solvent is evaporated and the crude product is distilled **(2)**[14] or recrystallized **(5)**. The purity is controlled by IR, $^1$H-, and $^{13}$C-NMR spectroscopy.

**Pyrroles 4; General Procedure:**

*Reaction of Silyl Enol Ethers* **1** *with N-Acylaminoacetone Acetal* **2**: In a dried, $N_2$-filled two-necked round-bottom flask fitted with a septum, $TiCl_4$ (760 mg, 4 mmol, 4 equiv) is added to a stirred solution of *N*-acetylaminoacetone dimethyl acetal (**2**; 161.2 mg, 1 mmol) in $CH_2Cl_2$ (10 mL) at −78 °C, immediately followed by a solution of the enol silyl ether (**1a–d**; 1 mmol, 1 equiv) in $CH_2Cl_2$ (1 mL). The mixture is stirred at −78 °C for 5 h, then hydrolysed with $H_2O$ (10 mL). The organic phase is washed with $H_2O$ (2 × 10 mL) and the aqueous phases with $CH_2Cl_2$ (2 × 10 mL). The combined organic phase are dried ($MgSO_4$), the solvent is evaporated, and the crude product **4** is isolated by chromatography on silica gel using hexane/EtOAc (5:1 to 1:1) as eluent. Products **4a** and **4b** are isolated as oils; product **4c** is recrystallized from hexane. Chromatography of the reaction products from **1b** and **2** in addition affords *methyl 7-acetylamino-6-methoxy-6-methyl-4-oxoheptanoate* **(3b)** as an oil; yield: 32 mg (12 %). From the reaction of **1d** with **2**, *2-(2-acetylamino-1-methoxy-1-methylethyl)cyclopentanone* **(3d)** is isolated as an oil as the only product; yield: 178 mg (83 %).

*Pyrroles* **4b** *and* **4d** *from the Aldol Products* **3b, d**: The aldol derivative **3b** or **3d** (1 mmol) is dissolved in benzene (3 mL) together with a catalytic amount of *p*-toluenesulfonic acid (5–10 mol %) and refluxed for 3 h over molecular sieves (~ 3 g) to remove the $H_2O$ formed. The solvent is evaporated and the crude product is chromatographed on a silica gel column using hexane/EtOAc (5:1 to 1:1) as eluent to give product **4b** as an oil whereas product **4d** solidifies upon distillation in a Kugelrohr apparatus [bp 60–70° (Kugelrohr oven)/0.02 Torr; mp 55–60 °C].

**2,3-Disubstituted 1-Methyl-5,10-dioxo-5,10-dihydropyrrolo[1,2-*b*]isoquinolines (7a, b):**

*Methyl 3-Acetyl-4-methoxy-4-methyl-5-phthalimidopentanoate* **(6a)** *and Methyl 6-Methoxy-6-methyl-4-oxo-7-phthalimidoheptanoate* **(6b)**: The aldol reaction between enol silyl ethers **1a/b** (3:1) and phthalimidoacetone dimethyl acetal **(5)** is performed as described above. The procedure affords product **6a** (as a mixture of two diastereoisomers), which can be crystallized from hexane/EtOAc (1:1), and product **6b** as an oil.

*Compounds* **7a** *and* **7b**: The aldol product **6a** or **6b** (1 mmol) is heated in a boiling mixture of MeOH (3 mL) and conc. HCl for 25 h. The resultant yellow crystalline product is isolated by suction and recrystallized from EtOH.

*Financial support from the Swiss National Science Foundation is acknowledged.*


(1) Battersby, A.R. *Natural Product Reports* **1987**, *4*, 77.
Battersby, A.R., McDonald, E. *Acc. Chem. Res.* **1979**, *12*, 14.
(2) Sundberg, R.J., in: Katritzky and Rees *Comprehensive Heterocyclic Chemistry*, Vol. 4, Bird, C.W., Cheeseman, G.W.H. (eds.), Pergamon Press, Oxford, 1984, p. 331.
(3) Gossauer, A. *Die Chemie der Pyrrole*, Springer-Verlag, Berlin, 1974, p. 309.
(4) Frydman, R.B., Frydman, B., Valassinas, A., in: *The Porphyrins*, Dolphin, D. (ed.), Academic Press, New York, 1979, Vol. VI, Part A, p. 33.
Barnard, G.F., Itoh, R., Hohberger, L.H., Shemin, D. *J. Biol. Chem.* **1977**, *252*, 8965.
(5) Sundberg, R.J., in: Katritzky and Rees *Comprehensive Heterocyclic Chemistry*, Vol. 4, Bird, C.W., Cheeseman, G.W.H. (eds.), Pergamon Press, Oxford, 1984, p. 353.
(6) Cipiciani, A., Savelli, G., Bunton, C.A. *J. Heterocycl. Chem.* **1984**, *21*, 975.
(7) Mukaiyama, T. *Angew. Chem.* **1977**, *89*, 858; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817.
Mukaiyama, T., Hayashi, M. *Chem. Lett.* **1976**, 279.
(8) Miller, R.D., McKean, D.R. *Synthesis* **1979**, 730.
(9) Torkelson, S., Ainsworth, C. *Synthesis* **1976**, 722.
(10) Taniguchi, Y., Inassaga, J., Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3229.
(11) Wilkinson, S.G., in: Barton and Ollis *Comprehensive Organic Chemistry*, Vol. 1, Stoddard, J.F. (ed.), Pergamon Press, Oxford, 1979, p. 624.
(12) Wiley, R.H., Borum, O.H. *J. Am. Chem. Soc.* **1948**, *70*, 2005.
(13) Lancaster, R.E., Van der Werf, C.A. *J. Org. Chem.* **1958**, *23*, 1208.
(14) Sato, T., Yamamoto, K., Fukui, K. *Chem. Lett.* **1973**, 111.
(15) Seibl, J. *Massenspektrometrie*, Akademische Verlagsgesellschaft, Frankfurt, 1970, p. 160.