SYNTHESIS
COMMUNICATIONS

Concise, complete papers on

- New or improved synthetic methods
- Key intermediates for organic synthesis

Including full experimental and analytical data

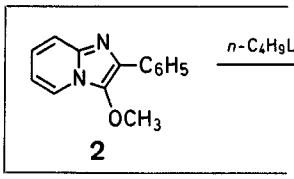
The Directed Lithiation of 3-Methoxy-2-phenylimidazo[1,2-*a*]pyridine

Allen J. GUILDFORD, Margaret A. TOMETZKI, Ralph W. TURNER*

Pharmaceuticals Division, Imperial Chemical Industries P.L.C., Alderley Park, Macclesfield, Cheshire, England

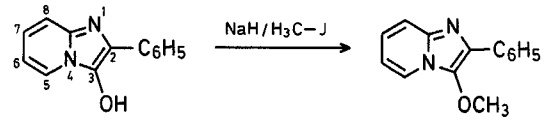
The ability of the methoxy group to facilitate the regioselective lithiation of aromatic and certain simple heterocyclic systems at a position *ortho* to the methoxy group has been well established[1,2,3]. In this article, we report the usefulness of the methoxy group in directing the 5-lithiation of 3-methoxy-2-phenylimidazo[1,2-*a*]pyridine **(2)**, permitting the sequential introduction of substituents into first the 5-position and then the 8-position of **2**.

The lithiation of the imidazo[1,2-*a*]pyridine ring system has received little attention[4,5,6]. The generation of anions either at position 5 or position 8 from 2,3-disubstituted imidazo[1,2-*a*]pyridines has not been reported, although the production of a mixture of 3,5-dilithio and 3,8-dilithio derivatives from 2-phenylimidazo[1,2-*a*]pyridine has been claimed[7].



2

Compound **2** was readily synthesised by reacting the sodium salt of 3-hydroxy-2-phenylimidazo[1,2-*a*]pyridine **(1)**[8] with methyl iodide in dimethylformamide.

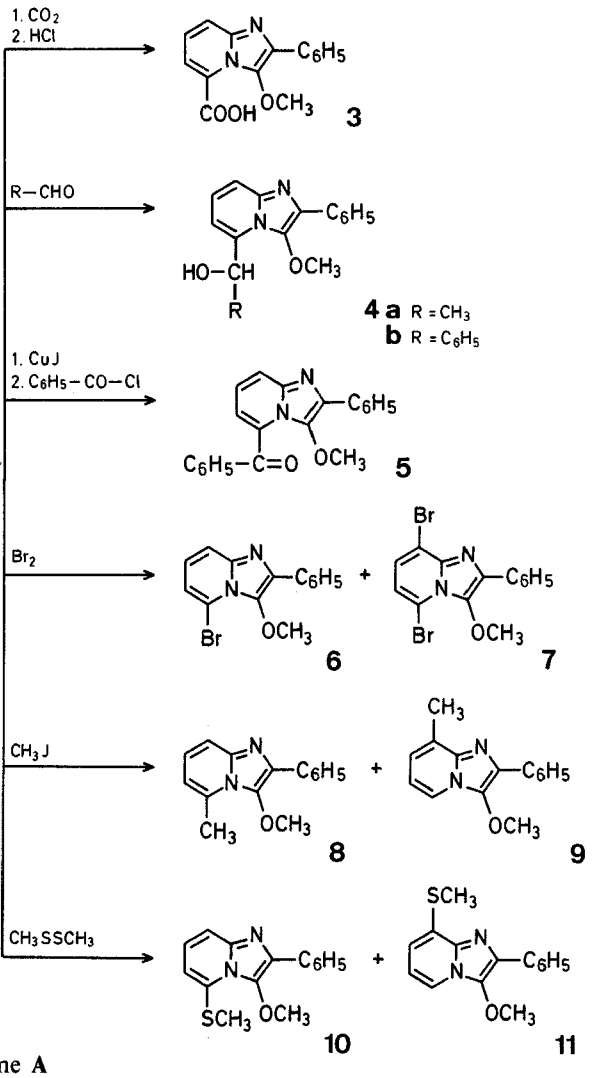


1 **2**

The ^{1}H-N.M.R. spectrum of **2** showed the C-5 ring proton as a doublet centred at $\delta = 7.9$ ppm and the C-7 and C-6 ring protons as complex triplets centred at $\delta = 7.0$ and 6.7 ppm, respectively[9-11]. The C-8 ring proton appeared together with three phenyl protons as a multiplet centred at $\delta = 7.4$ ppm, but was discernable as a doublet on addition of the shift reagent $Eu(fod)_3$. When **2** was treated with one equivalent of either *n*-butyllithium or lithium diisopropylamide at -70°C and the resultant anion quenched with deuterium oxide, the 5-deuterated derivative was the predominant product. ^{1}H-N.M.R. studies, utilising the characteristic C-5 proton doublet at $\delta = 7.9$ ppm as an index, indicated 95% deuteration. The same 5-deuterated compound was also obtained from **2** when two equivalents of lithium diisopropylamide were used.

A study of the reactions of the 5-lithiated derivative of **2** with a variety of electrophiles was undertaken (Scheme **A** and Table). Quenching the anion with carbon dioxide gave the 5-carboxylic acid derivative **3** in excellent yield. The ^{1}H-N.M.R. spectrum of **3** showed a predictable downfield shift for the C-6 proton. When acetaldehyde and benzaldehyde were utilised as the electrophile, the 5-substituted secondary alcohols **4a** and **4b** were obtained.

Benzoyl chloride reacted with the lithiated derivative of **2** to give a multiple component mixture. However, treatment of the organo-copper derivative of **2** with benzoyl chloride produced the required ketone **5** in 30% yield. Two products were obtained when bromine was used as the electrophile. The expected 5-bromo compound **6** was obtained in 63% yield together with a 6% yield of the 5,8-dibromoimidazo[1,2-*a*]pyridine **(7)**.



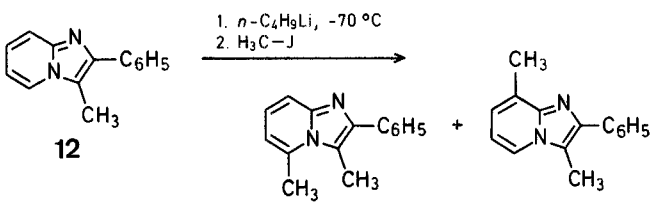
Scheme A

Finally, when the anion of **2** was quenched with either methyl iodide or dimethyl disulphide at -70°C, the expected 5-substituted derivatives **8** and **10** were isolated together with small amounts of their 8-substituted isomers **9** and **11**. None of the minor products **9** and **11** were formed if the anion was allowed to react with methyl iodide and dimethyl disulphide at 0°C.

These results would suggest that 3-methoxy-2-phenylimidazo[1,2-*a*]pyridine **(2)** undergoes kinetic deprotonation to give initially the 8-lithiated derivative, which rapidly reverts to the more stabilised 5-lithiated derivative. All attempts however, to enhance the production of

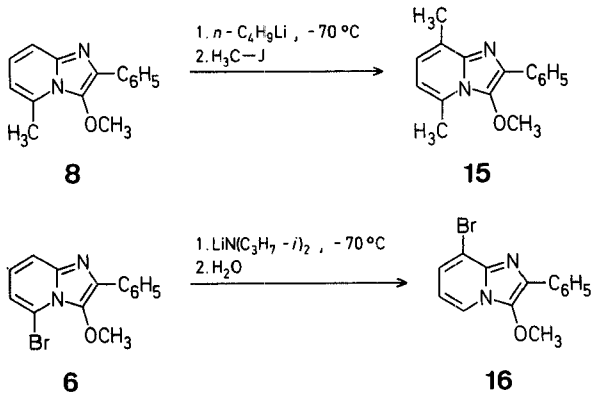
the 8-methylated product **9** by generating the lithium derivative of **1** at −110°C and quenching with methyl iodide at that temperature failed.

The facility with which the 3-methoxy group directs the lithiation of **2** was highlighted by contrasting the results recorded in the table with studies of the lithiation of 3-methyl-2-phenylimidazo[1,2*a*]pyridine **(12)**[12]. Lithiation of **12** with *n*-butyllithium at −70°C followed by reaction with methyl iodide gave 3,5-dimethyl-2-phenylimidazo[1,2-*a*]pyridine **(13)** in only 14% yield, the major product obtained was the isomeric 3,8-dimethyl-2-phenylimidazo[1,2-*a*]pyridine **(14)** in 69% yield (Scheme **B**).



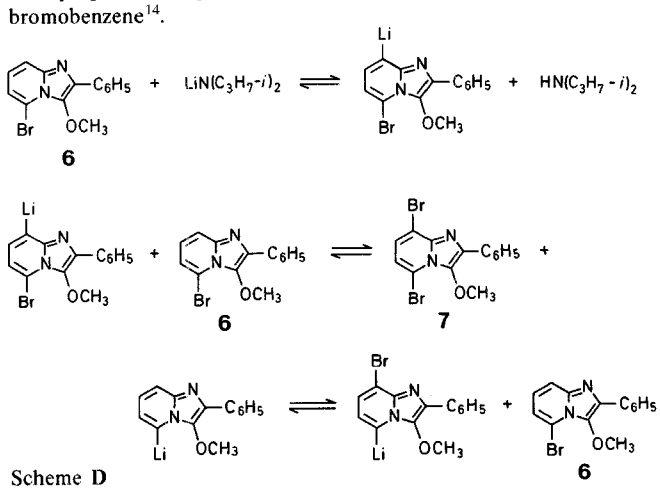
Scheme **B**

The lithiation of certain of the 5-substituted-3-methoxy-2-phenylimidazo[1,2-*a*]pyridines listed in the Table was then investigated. In the case of the 5-methyl derivative **8**, lithiation utilising *n*-butyllithium at −70°C, followed by reaction with deuterium oxide, gave the 8-deuterated compound as the sole product. When methyl iodide was used to quench the anion of **8**, 5,8-dimethyl-3-methoxy-2-phenylimidazo[1,2-*a*]pyridine **(15)** was obtained in 72% yield. Unexpectedly, when the 5-bromo compound **6** was treated with lithium diisopropylamide[13] at −70°C and the resultant anion was quenched with water, only a trace of starting material was detected. Instead the isomeric 8-bromo-3-methoxy-2-phenylimidazo[1,2-*a*]pyridine **(16)** was obtained in 60% yield.



Scheme **C**

The formation of **16** can be explained by a series of metal-halogen exchange equilibria (Scheme **D**), in which the 5-bromo compound **6** effectively catalysed the conversion of its anion to the stabilised 5-lithiated derivative of **16.** A similar "halogen dance" mechanism has been proposed to explain the base catalysed isomerisation of 1,2,4-tribromobenzene[14].



Scheme **D**

Table. Reaction of the Anion of **1** with Electrophiles

Product	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
3	77	193–194° (acetic acid)	$C_{15}H_{12}N_2O_3$ (268.3)	3.8 (s, 3H, OCH_3); 7.15 (m, 1H, 7-H); 7.25 (d, 1H, 6-H); 7.45 (m, 3H$_{arom}$); 7.65 (dd, 1H, 8-H); 8.0 (m, 2H$_{arom}$)
4a	80	152–153° (hexane/ toluene)	$C_{16}H_{16}N_2O_2$ (268.3)	1.5 (d, 3H, CH_3); 3.85 (s, 3H, OCH_3); 5.6 (m, 2H, CHOH); 7.1 (dd, 1H, 6-H); 7.45 (m, 5H, 7-H+8-H+H$_{arom}$); 8.1 (m, 2H$_{arom}$)[b]
4b	81	219–221° (DMF)	$C_{21}H_{18}N_2O_2$ (330.4)	3.7 (s, 3H, OCH_3); 6.25 (d, 1H, OH); 6.6 (d, 1H, CH); 6.95 (dd, 1H, 6-H); 7.35 (m, 10H, 7-H+8-H+H$_{arom}$); 7.95 (m, 2H$_{arom}$)
5	30	147–148° (ethyl acetate)	$C_{21}H_{16}N_2O_2$ (328.4)	3.6 (s, 3H, OCH_3); 6.85 (d, 1H, 6-H); 7.2 (m, 1H, 7-H); 7.5 (m, 7H, 8-H+H$_{arom}$); 7.9 (m, 4H$_{arom}$)
6	63	100–101° (hexane/ benzene)	$C_{14}H_{11}BrN_2O$ (287.2)	3.9 (s, 3H, OCH_3); 6.9 (m, 2H, 6-H+7-H); 7.4 (m, 4H, 8-H+H$_{arom}$); 8.15 (m, 2H$_{arom}$)
7	6	168–170° (ethanol)	$C_{14}H_{10}Br_2N_2O$ (382.1)	3.9 (s, 3H, OCH_3); 6.85 (dd, 1H, 6-H); 7.25 (dd, 1H, 7-H); 7.45 (m, 3H$_{arom}$); 8.2 (m, 2H$_{arom}$)
8	67	99–101° (hexane)	$C_{15}H_{14}N_2O$ (238.3)	2.8 (s, 3H, CH_3); 3.8 (s, 3H, OCH_3); 6.4 (m, 1H, 6-H); 6.9 (m, 1H, 7-H); 7.35 (m, 4H, 8-H+H$_{arom}$); 8.05 (m, 2H$_{arom}$)
9	8	87–88° (hexane)	$C_{15}H_{14}N_2O$ (238.3)	2.6 (s, 3H, CH_3); 3.9 (s, 3H, OCH_3); 6.6 (m, 1H, 6-H); 6.9 (d, 1H, 7-H); 7.4 (m, 3H$_{arom}$); 7.8 (d, 1H, 5-H); 8.1 (m, 2H$_{arom}$)
10	64	99–100° (hexane/ benzene)	$C_{15}H_{14}N_2OS$ (270.4)	2.5 (s, 3H, SCH_3); 3.9 (s, 3H, OCH_3); 6.4 (d, 1H, 6-H); 6.95 (m, 1H, 7-H); 7.35 (m, 4H, 8-H+H$_{arom}$); 8.1 (m, 2H$_{arom}$)
11	6	130–131° (ethanol)	$C_{15}H_{14}N_2OS$ (270.4)	2.55 (s, 3H, SCH_3); 3.9 (s, 3H, OCH_3); 6.7 (m, 1H, 6-H); 6.8 (dd, 1H, 7-H); 7.35 (m, 3H$_{arom}$); 7.75 (dd, 1H, 5-H); 8.1 (m, 2H$_{arom}$)

[a] Satisfactory microanalyses obtained: C, ±0.3; H, ±0.1; N, ±0.3; Br, ±0.3; S, ±0.3.

[b] Measured in DMSO-d_6.

In summary, we have demonstrated that a methoxy group can effectively direct lithiation and facilitate the sequential introduction of substituents into the 5-position and then the 8-position of the imidazo[1,2-*a*]pyridine ring system. The related thioalkyl group directed 5-lithiation in 3-ethylthioimidazo[1,5-*a*]pyridine system[15] and our method are useful synthetic manipulations for medicinal chemists. Further studies in this direction of structure-activity relationship are in progress.

Melting points are uncorrected and were determined on a Reichert apparatus. ^{1}H-N.M.R. spectra were obtained on a Varian EM390 instrument. Merck silica gel 60 (70–230 mesh) was used throughout for column chromatography.

3-Methoxy-2-phenylimidazo[1,2-*a*]pyridine (2):
A slurry of **1** (24.0 g, 0.114 mol) in dry dimethylformamide (200 ml) is degassed with nitrogen under stirring and then kept under a positive nitrogen flow. Sodium hydride (6.1 g, 0.127 mol) is added gradually, keeping the reaction temperature below 35°C. After 10 min, methyl iodide (18.03 g, 0.127 mol) is gradually added at below 35°C. The mixture is further stirred for 15 min and water (400 ml) is added. The aqueous phase is extracted with ethyl acetate (2 × 400 ml), the extract is dried with magnesium sulfate, and evaporated to dryness. The crude product is purified by chromatography on silica gel with toluene/ethyl acetate (10:3) as eluent; yield: 15.0 g (60%); m.p. 104–105°C (toluene/hexane).

$C_{14}H_{12}N_2O$	calc.	C 74.99	H 5.38	N 12.49
(224.3)	found	75.3	5.4	12.7

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.85$ (s, 3H, OCH_3); 6.7 (t, 1H, 6-H); 7.0 (t, 1H, 7-H); 7.4 (m, 4H, 8-H + H_{arom}); 7.9 (d, 1H, 5-H); 8.05 ppm (m, 2H_{arom}).

Reaction of the Anion of 2 with Electrophiles; General Procedure:
A 1.6 mmol solution of *n*-butyllithium in hexane (6.56 ml, 10.5 mmol) is added dropwise over 10 min to a stirred solution of **2** (2.24 g, 10 mmol) in dry tetrahydrofuran (22 ml) at −70°C under an argon atmosphere. The mixture is stirred for 30 min and the appropriate electrophile (10.5 mmol; Table, for exceptions, see below) is added gradually over 5 min at −70°C. The cooling bath is removed and the mixture is then extracted with ether (3 × 100 ml), the extract is dried with magnesium sulphate, and evaporated to give the crude product. Compounds **2, 3,** and **4** are purified by recrystallisation (Table).

The products from *bromine, methyl iodide,* and *dimethyl disulphide* as electrophiles are separated by chromatography on silica gel with toluene/ethyl acetate (9:1 in the case of bromine and methyl iodide, 5:1 in the case of dimethyl disulphide) as eluent.

With *carbon dioxide* as electrophile: In this case the tetrahydrofuran solution of the anion is swept by a pressure of argon through a canula into a stirred slurry of excess of carbon dioxide in dry ether (10 ml) and maintained at −70°C. After the reaction, the mixture is acidified with 1 normal hydrochloric acid to pH = 2 and worked-up as above.

With *benzoyl chloride* as electrophile: To the anion of **2** (10 mmol; prepared as described above) is added copper(I) iodide (0.95 g, 5 mmol) under argon at −70°C and the mixture is stirred for 1 h. The general procedure is then implemented utilising benzoyl chloride (1.405 g, 10 mmol). The crude product is purified by preparative T.L.C. (Merck silica gel plates, 2 mm) with ethyl acetate as eluent.

3,5- and 3,8-Dimethyl-2-phenylimidazo[1,2-*a*]pyridine (13 and 14):
A 1.6 molar solution of *n*-butyllithium in hexane (10.8 ml, 17 mmol) is added dropwise over 10 min to a stirred solution of **12** (3.12 g, 15 mmol) in dry tetrahydrofuran (46 ml) at −70°C under argon. After stirring for 30 min, methyl iodide (2.49 g, 17.5 mmol) is added over 5 min at −70°C. The mixture is stirred at −70°C for 1 h and then at ambient temperature for 1 h. Water (100 ml) is added and the product is extracted with ether (3 × 200 ml). The combined extracts are dried with magnesium sulphate and the solvent removed. Column chromatography on silica gel using toluene/ethyl acetate (9:1) as eluent gives first compound **14** as a colourless oil; yield: 2.3 g (69%).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.6$ (s, 3H, CH_3): 2.65 (s, 3H, CH_3): 6.75 (t, 1H, 6-H); 7.0 (dd, 1H, 7-H); 7.3 (m, 3H_{arom}); 7.8 ppm (m, 3H, 5-H + H_{arom}).

Compound **14** is also characterised as its hydrochloride salt; m.p. 215–216°C (ether/ethanol).

$C_{15}H_{15}ClN_2$	calc.	C 69.63	H 5.84	N 10.83
(258.8)	found	69.6	5.7	10.8

Further elution gives compound **13**; yield: 0.47 g (14%); m.p. 89–90°C (hexane/ethyl acetate).

$C_{15}H_{14}N_2$ calc.	calc.	C 81.05	H 6.35	N 12.60
(222.3)	found	81.2	6.4	12.4

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.9$ (s, 6H, CH_3); 6.45 (d, 1H, 6-H); 6.95 (dd, 1H, 7-H); 7.4 (m, 4H, 3H_{arom} + 8-H); 7.6 ppm (m, 2H_{arom}).

5,8-Dimethyl-3-methoxy-2-phenylimidazo[1,2-*a*]pyridine (15):
A 1.6 molar solution of *n*-butyllithium in hexane (6.56 ml, 10.5 mmol) is added dropwise over a period of 10 min to a stirred solution of **8** (2.38 g, 10 mmol) in dry tetrahydrofuran (25 ml) at −70°C under argon. After 1 h, methyl iodide (1.49 g, 10.5 mmol) is added, the mixture is further stirred for 1 h at −70°C and then 1 h at room temperature. Water (100 ml) is added and the product extracted with ether (3 × 100 ml). The ether extract is dried with magnesium sulphate and evaporated to give a gum, which is purified by column chromatography on silica gel. Elution with toluene/ethyl acetate (19:1) gives **15**; yield: 1.8 g (72%); m.p. 99–100°C (hexane).

$C_{16}H_{16}N_2O$	calc.	C 76.17	H 6.39	N 11.10
(252.3)	found	75.9	6.5	10.8

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.55$ (s, 3H, CH_3); 2.7 (s, 3H, CH_3); 3.75 (s, 3H, OCH_3); 6.3 (d, 1H, 6-H); 6.7 (d, 1H, 7-H); 7.35 (m, 3H_{arom}); 8.1 ppm (m, 2H_{arom}).

8-Bromo-3-methoxy-2-phenylimidazo[1,2-*a*]pyridine (16):
A 1.6 molar solution of *n*-butyllithium in hexane (5.36 ml, 8.6 mmol) is added dropwise over 5 min 60 a stirred solution of dry isopropylamine (0.87 g, 8.6 mmol) in dry tetrahydrofuran (25 ml) at 0°C under argon. After stirring for 30 min at 0°C, this solution is introduced through a canula into a stirred solution of **6** (2.5 g, 8.25 mmol) in dry tetrahydrofuran (25 ml) at −70°C under argon. After stirring for 30 min at −70°C, water (10 ml) is added, the cooling bath removed and allowed to come to room temperature. The product is extracted with ether (3 × 100 ml), the ether phase is dried with magnesium sulphate and evaporated to give a yellow gum. Purification by column chromatography on silica gel using toluene/ethyl acetate (19:1) as eluent gives **16**; yield: 1.5 g (60%); m.p. 134–136°C (isopropanol).

$C_{14}H_{11}BrN_2O$	calc.	C 55.46	H 3.66	N 9.24
(303.2)	found	55.1	3.6	9.4

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.9$ (s, 3H, OCH_3); 6.65 (t, 1H, 6-H); 7.4 (m, 4H, 7-H + H_{arom}); 7.9 (dd, 1H, 5-H); 8.1 ppm (m, 2H_{arom}).

Received: June 13, 1983

1 D. W. Slocum, C. A. Jennings, *J. Org. Chem.* **41,** 3653 (1976).
2 B. J. Wakefield, *The Chemistry of Organolithium Compounds*, Pergamon Press, London, 1974, p. 39.
3 J. M. Mallan, R. L. Bebb, *Chem. Rev.* **69,** 693 (1969).
4 W. W. Paudler, L. S. Helmuck, *J. Org. Chem.* **33,** 1087 (1968).
5 W. W. Paudler, H. G. Shin, *J. Org. Chem.* **33,** 1638 (1968).
6 Y. Goldfarb, S. N. Godovikova, *Izv. Akad. Nauk SSSR, Ser. Khim.* **9,** 1671 (1965); *C. A.* **64,** 3508 (1966).
7 S. N. Godovikova, V. Sheichenko, *Khim. Geterotsikl. Soedin. Sb. 1: Azotsoderzhashchie Geterotsikly* **1967,** 175 *C. A.* **70,** 77908 (1969).
8 S. Inoue, S. Sugiura, H. Kakoi, T. Goto, *Tetrahedron Lett.* **1969,** 1609.
9 W. W. Paudler, H. L. Blewitt, *Tetrahedron* **21,** 353 (1965).
10 J. P. Paolini, R. K. Robins, *J. Heterocyclic Chem.* **2,** 53 (1965).
11 P. J. Black, M. L. Hefferman, L. M. Jackman, Q. N. Porter, G. R. Underwood, *Aust. J. Chem.* **17,** 1128 (1964).
12 M. H. Fisher, A. Lusi, *J. Med. Chem.* **15,** 982 (1972).
13 Lithium diisopropylamide facilitates specific halogen-metal metal exchange reactions: G. M. Davies, P. S. Davies, *Tetrahedron Lett.* **1972,** 3507.
14 J. F. Bunnett, *Acc. Chem. Res.* **5,** 139 (1972).
15 P. Blatcher, D. Middlemass, *Tetrahedron Lett.* **21,** 2195 (1980).