OCH_2Ph), 4.18 (d, 2, J = 12.5 Hz, $ArCH_2Ar$), 4.14 (d, 2, J = 12.5 Hz, $ArCH_2Ar$), 3.04 (d, 2, J = 12.5 Hz, $ArCH_2Ar$), 2.98 (d, 2, J = 12.5 Hz, $ArCH_2Ar$), 1.32 (s, 9, CMe_3), 1.29 (s, 9, CMe_3), 0.83 (s, 18, CMe_3). Anal. Calcd for $C_{65}H_{74}O_4 \cdot {}^1/_3CH_2Cl_2$: C, 83.33; H, 7.98. Found: C, 83.04; H, 8.00. In addition, 5% of $\mathbf{4a_c}$ and 12% of starting material ($\mathbf{5_c}$) were isolated in the chromatographic separation.

Partial Cone Conformer of 5,11,17,23-Tetra-*tert*-butyl-25,26,27-tris(benzyloxy)-28-hydroxycalix[4]arene ($\mathbf{9_{pc}}$). To a stirred and ice-bath-cooled mixture of 0.828 g (1 mmol) of dibenzyl ether $\mathbf{5_c}$ and 0.171 g (1.2 mmol) of $KOSiMe_3$ (90% pure) in an atmosphere of N_2, was added dropwise a solution of 0.188 g (1.1 mmol) of benzyl bromide in 20 mL of THF, and the mixture was stirred at room temperature for 15 h. The solvent was then removed under vacuum, the residue was treated with 100 mL of 1 N HCl, and the gummy residue was extracted into CH_2Cl_2, which was washed with water and brine, dried over Na_2SO_4, and evaporated to give 0.68 g of a white powder. Column chromatography produced (a) 0.095 g (9%) of **4a**, the ^1H NMR spectrum of which indicated it to be an 89:11 mixture of $\mathbf{4a_{pc}}$ and $\mathbf{4a_{1,3\text{-}alt}}$; (b) 0.08 g (10%) of $\mathbf{5_{pc}}$, described below; and (c) 0.435 g (47%) of $\mathbf{9_{pc}}$, obtained as white needles after recrystallization from $CHCl_3$–MeOH: mp 182–185 °C; ^1H NMR ($CDCl_3$) δ 7.39–7.28 (m, 9, ArH), 7.19 (s, 1, OH), 7.10 (s, 2, ArH), 7.04 (s, 2, ArH), 6.90–6.67 (m, 8, ArH), 6.21 (d, 2, J = 7.5 Hz, ArH), 5.09 (d, 2, J = 12.0 Hz, OCH_2Ph), 4.71 (d, 2, J = 12.0 Hz, OCH_2Ph), 4.03 (d, 2, J = 12.9 Hz, $ArCH_2Ar$), 3.90 (d, 2, J = 15.3 Hz, $ArCH_2Ar$), 3.83 (d, 2, J = 15.3 Hz, $ArCH_2Ar$), 3.80 (s, 2, OCH_2Ph), 3.10 (d, 2, J = 12.9 Hz, $ArCH_2Ar$), 1.32 (s, 9, CMe_3), 1.01 (s, 9, CMe_3), 0.77 (s, 18, CMe_3). Anal. Calcd for $C_{65}H_{74}O_4$: C, 84.64; H, 7.99. Found: C, 84.93; H, 8.11.

Partial Cone Conformer of 5,11,17,23-Tetra-*tert*-butyl-25,27-bis(benzyloxy)-26,28-dihydroxycalix[4]arene ($\mathbf{5_{pc}}$). As described above, $\mathbf{5_{pc}}$ was isolated in 10% yield from a reaction of $\mathbf{5_c}$ with benzyl bromide and $KOSiMe_3$ and was obtained as colorless crystals after recrystallization from $CHCl_3$–MeOH: mp 239–241 °C; ^1H NMR ($CDCl_3$) δ 8.29 (s, 2, OH), 7.13 (d, 2, J = 2.3 Hz, ArH), 6.96–6.75 (m, 12, ArH), 6.22 (d, 4, J = 7.8 Hz, ArH), 4.72 (d, 2, J = 11.6 Hz, OCH_2Ph), 4.41 (d, 2, J = 11.6 Hz, OCH_2Ph), 4.07 (s, 2, $ArCH_2Ar$), 3.84 (s, 4, $ArCH_2Ar$), 3.68 (s, 2, $ArCH_2$ Ar), 1.01 (s, 36, CMe_3) (in DMSO-d_6 this signal splits into two singlets of equal intensity at δ 0.99 and 0.96); ^{13}C NMR ($CDCl_3$) δ 151.53, 149.10, 147.05, 142.65, 136.35, 133.68, 132.09, 128.51, 127.79, 127.30, 126.19, 125.35, 125.08, 124.36, 72.16 ($ArCH_2O$), 39.95 ($ArCH_2Ar$), 33.87 ($ArCH_2Ar$), 33.60 ($ArCH_2Ar$), 32.40 (CMe_3), 31.26 (CMe_3), 31.16 (CMe_3). Anal. Calcd for $C_{58}H_{68}O_4 \cdot {}^1/_4CHCl_3$: C, 82.71; H, 8.13. Found: C, 82.84; H, 8.08. A reaction carried out with $\mathbf{5_c}$ as described above but in the absence of benzyl bromide failed to yield any $\mathbf{5_{pc}}$ and gave only recovered starting material.

Benzylation Reactions. (a) The procedures described above for the preparation of $\mathbf{4a_c}$ were used to carry out reactions involving changes in time, temperature, solvent, and benzyl halide, giving the data recorded in Tables I and II. (b). The general procedures described above were followed in treating compounds **2**, $\mathbf{5_c}$, $\mathbf{5_{pc}}$, $\mathbf{9_c}$, and $\mathbf{9_{pc}}$ with benzyl bromide in the presence of NaH, K_2CO_3, or $KOSiMe_3$ in acetone or THF–DMF. The product mixtures were assayed to give the results shown in Table V, where the percentage yields represent in all but two instances the amount of isolated, purified material.

Acknowledgment. We are indebted to the National Institutes of Health (GM-23534) and the Robert A. Welch Foundation (P-1163) for generous support of this research.

Notes

Photoinduced Phosphorylation by [α-(Hydroxyimino)benzyl]phosphonates through Fragmentation to Monomeric Metaphosphates

Eli Breuer* and Mahmoud Mahajna

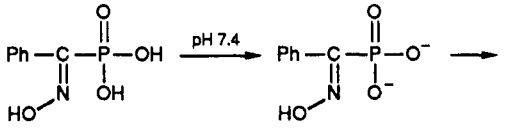
Department of Pharmaceutical Chemistry, The School of Pharmacy, The Hebrew University of Jerusalem, Jerusalem, 91120 Israel

Louis D. Quin* and Gyöngyi S. Quin

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003

Received December 27, 1990 (Revised Manuscript Received March 23, 1991)

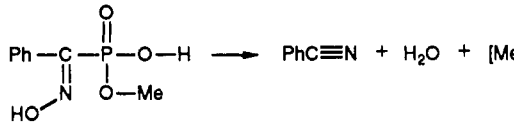
Previously it was reported from one of our laboratories that α-hydroxyimino phosphonic acids and monoesters can serve as precursors to monomeric metaphosphate anion[1] or to alkyl metaphosphates,[2] respectively, and consequently may act as phosphorylating agents. Thus, [α-(hydroxyimino)benzyl]phosphonic acid (**1a**) is unstable as the free acid or as a salt and undergoes facile fragmentation at physiological pH (eq 1).[1] The corresponding monoesters



1a

$$PhC{\equiv}N + OH^- + PO_3^- \quad (1)$$

(e.g., **1b**) are unstable as free acids which undergo spontaneous fragmentation as shown in eq 2. Their salts are



$$PhC{\equiv}N + H_2O + [MeOPO]_2 \quad (2)$$

1b

stable[2] but are unsuitable for use as reagents in organic solvents because of their lack of solubility. Their conversion in situ to the active **1b** would require acid treatment, which could be harmful to some substrates to be phosphorylated. One possible way to avoid this would employ α-hydroxyimino phosphonates with photolabile ester groups,[3] which would liberate the active compounds on irradiation. Benzyloxy groups on phosphorus are

(1) Breuer, E.; Karaman, R.; Gibson, D.; Leader, H.; Goldblum, A. *J. Chem. Soc., Chem. Commun.* **1988**, 504.

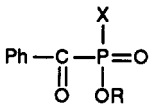
(2) (a) Breuer, E.; Karaman, R.; Leader, H.; Goldblum, A. *J. Chem. Soc., Chem. Commun.* **1987**, 671. (b) Katzhendler, J.; Karaman, R.; Gibson, D.; Breuer, E.; Leader, H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 589.

(3) Kirby, A. J.; Varvoglis, A. G. *Chem. Commun.* **1967**, 405, 406. Rubinstein, M.; Amit, B.; Patchornik, A. *Tetrahedron Lett.* **1975**, 1445. Epstein, W. W.; Garrossian, M. *J. Chem. Soc., Chem. Commun.* **1987**, 532. Walker, J. W.; Reid, G. P.; McCray, J. A.; Trentham, D. R. *J. Am. Chem. Soc.* **1988**, *110*, 7170.

0022-3263/91/1956-4791$02.50/0 © 1991 American Chemical Society

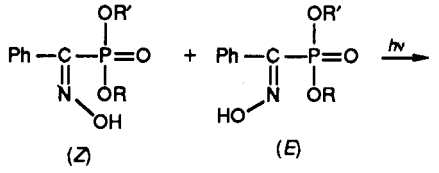
known to be cleaved on UV irradiation;[4] in this paper we report the synthesis of some benzyl esters of [α-(hydroxyimino)benzyl]phosphonic acid and their utility in photoinduced phosphorylation, through fragmentation to monomeric metaphosphates.

Methyl hydrogen benzoylphosphonate[5] (2) was converted to methyl benzoylphosphonochloridate (3) by reaction with thionyl chloride. Compound 3 was allowed to react with o-nitrobenzyl alcohol, or with benzyl alcohol, in dichloromethane in the presence of N,N-diethylaniline to yield methyl o-nitrobenzyl (NBn) benzoylphosphonate (4a) or benzyl (Bn) methyl benzoylphosphonate (4b), respectively. Ketones 4a and 4b were converted, by



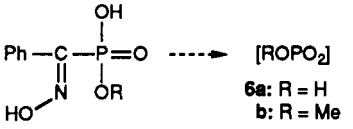
2: X = OH; R = Me
3: X = Cl; R = Me
4a: X = ONBn; R = Me
4b: X = OBn; R = Me
4c: X = OBn; R = Bn

treatment with hydroxylamine, to the geometrical isomers of the corresponding oximes 5a and 5b. Irradiation of 5a



(Z) (E)

5a: R = Me; R′ = NBn
b: R = Me; R′ = Bn
c: R = Bn; R′ = Bn
d: R = Me; R′ = Me



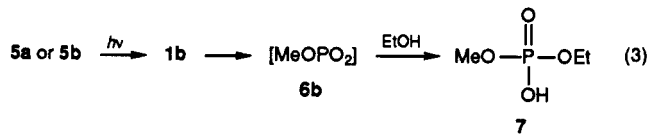
1a: R = H
b: R = Me

6a: R = H
b: R = Me

at 254 nm in absolute ethanol in a quartz apparatus[6] described elsewhere[7] gave ethyl methyl hydrogen phosphate in over 90% yield. Identical results were obtained when 5a was irradiated in dioxane containing 5 equiv of ethanol. Further investigation revealed that identical results can be obtained when the o-nitrobenzyl group is replaced by the simpler benzyl group. Thus irradiation of benzyl methyl [α-(hydroxyimino)benzyl]phosphonate 5b (as a 1:1 mixture of E, Z isomers) either in ethanol or in dioxane containing 5 equiv of ethanol gave ethyl methyl hydrogen phosphate (7) as a single product.

The formation of ethyl methyl hydrogen phosphate in these experiments shows that under the influence of light 5a and 5b suffered debenzylation to methyl hydrogen [α-(hydroxyimino)benzyl]phosphonate (1b). The latter then fragmented to methyl metaphosphate (6b), which in turn phosphorylated ethanol (eq 3).

While these results indicate that reagents such as 5a and 5b can be used for the synthesis of phosphodiesters under

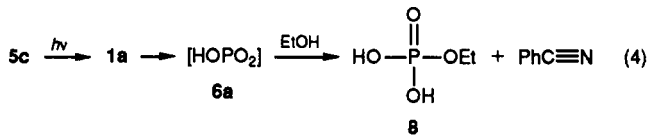


7

(3)

mild conditions, the greater challenge is in the direct synthesis of phosphomonoesters under mild conditions compatible with biological systems. Among the known chemical methods for phosphorylation, only potassium phosphoramidate was reported to be useful at physiological pH; all other phosphoric acid derivatives belong to the phosphorochloridate or phosphoric anhydride type.[8] Other reagents are based on P(III) chemistry and require anhydrous conditions and an oxidation step.[9]

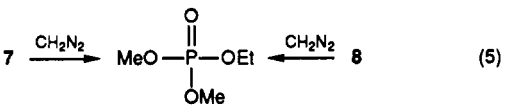
To achieve phosphomonoester synthesis by our methodology, we irradiated dibenzyl [α-(hydroxyimino)benzyl]phosphonate (5c, E:Z = 8:2, synthesized similarly to 5a and 5b) either in ethanol (6 h) or in dioxane containing 5 equiv of ethanol (9 h). These experiments gave, via the consecutive intermediacy of 1a and of metaphosphoric acid (6a), ethyl dihydrogen phosphate (8), and benzonitrile (eq 4) in nearly quantitative yields.[10] The



8

(4)

loss of the benzyl group(s) during irradiation of 5a and 5c was further confirmed by gas chromatography–mass spectrometry. Reaction of the photoproducts 7 or 8 with diazomethane gave identical products (eq 5) identified as dimethyl ethyl phosphate (9) by GC–MS through the $M^+ - 1$ peak of $m/z = 153$, which is typical of simple phosphates.[13]



9

(5)

In a control experiment, 5c was irradiated in acetonitrile or propionitrile, in the absence of alcohols. We observed the appearance of complex ^{31}P NMR signals around −10 and −21 ppm. These indicate the formation of dimeric and trimeric polyphosphates from a metaphosphate intermediate. Also, when dimethyl (E)-[α-(hydroxyimino)benzyl]phosphonate (5d),[14] which lacks a photolabile benzyl O-substituent, was irradiated in ethanol, a very complex mixture of decomposition products was formed that contained little, if any, alkyl phosphate.

In conclusion, our results show that benzyl α-hydroxyimino phosphonates serve as efficient precursors to the corresponding acids on photolysis, and as a consequence

(4) Givens, R. S.; Matuszewski, B. *J. Am. Chem. Soc.* **1984**, *106*, 6860.
(5) Karaman, R.; Goldblum, A.; Breuer, E.; Leader, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 765.
(6) In a control experiment 5c was irradiated in a Pyrex vessel for 12 h; no fragmentation was observed.
(7) Quin, L. D.; Pete, B.; Szewczyk, J.; Hughes, A. N. *Tetrahedron Lett.* **1988**, *29*, 2627.
(8) Frank, A. W. *Phosphorus Sulfur* **1987**, *29*, 297; *CRC Crit. Revs. Biochem.* **1984**, *16*, 51.
(9) Bannwarth, W.; Trzeciak, A. *Helv. Chim. Acta* **1987**, *70*, 175.
(10) It is worthy to note another recently reported photochemical method assumed to generate metaphosphate anion, by the irradiation of (p-nitrobenzyl)phosphonate dianion[11] or (triarylmethyl)phosphonate dianion.[12]
(11) Okamoto, Y.; Iwamoto, N.; Toki, S.; Takamuku, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 277.
(12) Shi, M.; Okamoto, Y.; Takamuku, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 453.
(13) Desmarchelier, J. M. S.; Wustner, D. A.; Fukuto, T. R. *Residue Rev.* **1976**, *63*, 77.
(14) Breuer, E.; Karaman, R.; Goldblum, A.; Gibson, D.; Leader, H.; Potter, B. V. L.; Cummins, J. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3047.

they can now be used for the design of novel, mild phosphorylating agents, possibly of use at physiological pH.

Experimental Section[15]

Methyl Benzoylphosphonochloridate (3). To methyl hydrogen benzoylphosphonate[5] (2, 20 g, 0.1 mol) in dry dichloromethane (70 mL) was added dropwise freshly distilled thionyl chloride (11.9 g, 7.3 mL, 0.1 mol). After the reaction mixture had been stirred for 3 h at ambient temperature, the solvent was evaporated to afford 3 as an unstable oil. It was identified by its ^{31}P NMR chemical shift (δ 14.4) and the coupling of this signal with ^{1}H (q) and used immediately without further purification.

Methyl *o*-Nitrobenzyl Benzoylphosphonate (4a). To a solution of 3 (21.8 g, 0.1 mol) in dry dichloromethane (70 mL), stirred under nitrogen at 0 °C, was added dropwise a solution of *N,N*-diethylaniline (17.5 mL, 0.11 mol) and *o*-nitrobenzyl alcohol (15.3 g, 0.1 mol) in dry dichloromethane (70 mL) over a period of 30 min. After the reaction mixture had been stirred for 3 h at ambient temperature, the solvent was removed at reduced pressure and the residue was taken up in anhydrous ether. *N,N*-Diethylanilinium chloride was removed by filtration; evaporation of the ether yielded 30 g (90%) of crude 4a as an oil: δ ^{31}P ($CDCl_3$) -1.8 (sext); IR (neat) CH 3050, C=O 1656, C=C 1594, P=O 1260 cm^{-1}. This product was used immediately without further purification for the synthesis of oxime 5a, which served as a derivative for analysis.

Methyl Benzyl Benzoylphosphonate (4b). A procedure identical with that used to prepare 4a was followed (crude yield 90%): IR (neat) CH 3050, C=O 1650, C=C 1594, P=O 1270, POC 1047 cm^{-1}; δ ^{31}P ($CDCl_3$) -1.4 (sext). This product was used immediately without further purification for the synthesis of the oxime derivative 5b.

Dibenzyl Benzoylphosphonate (4c). To benzoyl chloride (14 g, 0.1 mol) cooled to 0 °C was added 35.2 g of tribenzyl phosphite[16] dropwise with stirring at such a rate that the temperature of the reaction mixture remained below 10 °C. After all of the phosphite had been added, the reaction mixture was stirred for 3 h at ambient temperature. The excess benzoyl chloride was removed by vacuum distillation (60 °C at 1 mm) to leave dibenzyl benzoylphosphonate as a crude (80%) oil: δ ^{31}P ($CDCl_3$) -1.25 (quint). Dibenzyl benzylphosphonate (20%, δ ^{31}P 16.9) was also formed from Arbusov reaction of benzoyl chloride (generated in the initial reaction) with tribenzyl phosphite. The product mixture was used without further purification for the synthesis of the oxime derivative 5c.

Dibenzyl [α-(Hydroxyimino)benzyl]phosphonate (5c). Dibenzyl benzoylphosphonate (4c, 36.6 g, 0.1 mol) was added to a solution of hydroxylamine hydrochloride (8.3 g, 0.12 mol) and dry pyridine (10.5 mL, 0.13 mol) in absolute methanol (100 mL). After the reaction mixture had been stirred for 5 h, the methanol was evaporated under reduced pressure to yield a syrup, which was taken up in 1 M HCl (50 mL). The aqueous mixture was extracted with chloroform (4 × 75 mL), and the combined extracts were washed with water (100 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica. After the elution of dibenzyl benzylphosphonate and dibenzyl phosphonate (side product obtained via C-P bond cleavage in 4c) by chloroform, the product 5c (a 8:2 mixture of *E, Z* isomers) was eluted with 5% methanol in chloroform: yield 22.5 g (60%); mp 79-80 °C; NMR ($CDCl_3$) δ ^{31}P 9.6 (*E*-5c), 5.5 (*Z*-5c); δ ^{1}H 5.05 (broad, 4 H), 7.49-7.18 (m, 15 H). Anal. Calcd for $C_{21}H_{20}NO_4P$: C, 66.14; H, 5.25. Found: C, 65.99; H, 5.31.

Methyl *o*-Nitrobenzyl [α-(Hydroxyimino)benzyl]phosphonate (5a). This compound was prepared as a *E-Z* mixture (solid) and purified as described for 5c: NMR ($CDCl_3$) δ ^{31}P 10.1 (80% *E*-5a), 6.4 (20% *Z*-5a); ^{1}H δ 3.83 and 3.82 (both d, J = 12 Hz, total 3 H), 5.55 (broad, 2 H), 7.56-7.32 (m, 9 H), 8.08 (d, J = 8.4 Hz, 1 H). Anal. Calcd for $C_{15}H_{15}N_2O_6P$: C, 51.42; H, 4.28; N, 8.0. Found: C, 51.57; H, 4.35; N, 7.91.

Methyl Benzyl [α-(Hydroxyimino)benzyl]phosphonate (5b). This compound (*E-Z* mixture, oil) was prepared and purified as described for 5c: NMR ($CDCl_3$) δ ^{31}P 10.4 (50%, *E*-5b), 6.6 (50%, *Z*-5b); ^{1}H δ 3.83 and 3.82 (both d, J = 12 Hz, total 3 H), 5.01 (broad, 2 H), 7.55-7.34 (m, 10 H). Anal. Calcd for $C_{15}H_{16}NO_4P$: C, 59.01; H, 5.24; N, 4.59. Found: C, 59.11; H, 5.23; N, 4.71.

Irradiation Experiments. Solutions of 5a or 5b (0.008 M in absolute ethanol or in dioxane containing 5 equiv of ethanol) were irradiated with a Hanovia 450-W medium-pressure lamp (nominally 254 nm) at room temperature for 5 h, in a quartz apparatus[6] described elsewhere.[7] These reactions gave ethyl methyl hydrogen phosphate (7, δ ^{31}P 0.25) in over 90% yield (determined by ^{31}P NMR). Similarly, irradiation of 5c gave ethyl dihydrogen phosphate (8, δ ^{31}P 0.12) in nearly quantitative yields. In all experiments the formation of benzonitrile was observed by GC and IR.

Gas Chromatography-Mass Spectrometry of the Irradiation Products. Samples obtained from the two irradiation experiments were subjected to methylation with diazomethane (generated from Diazald). The products had the same ^{31}P NMR spectrum (δ +1.25, $CDCl_3$) and GC retention time (4.05 min) on a 25 m × 0.21 mm i.d. column of DB-5 (temperature program 60 °C per min for 1 min, then 15 °C per min, injector 260 °C). By using an atomic emission GC detector set at the frequency for phosphorus (186 nm), it was shown that the only significant phosphorus-containing product was that with retention time 4.05 min. The MS detector confirmed that this product (9) was identical whether originated from either 5a or 5c. MS: $M^+ - 1$ (2.4) m/z 127 (100, $M^+ - C_2H_3$), 110 (19.2), 96 (24.2), 79 (15.5).

Acknowledgment. This research was supported, in part, by Grant No. 86-00021 from the United States-Israel Binational Science Foundation (B.S.F.), Jerusalem, Israel (to E.B.), and in part by the U.S. Army Research Office (to L.D.Q.). M.M. thanks B.S.F. for a travel grant, which made it possible to carry out most of this work in Amherst.

(15) ^{31}P NMR shifts (FT, ^{1}H decoupled) are referenced to 85% H_3PO_4; positive shifts are downfield. The multiplicity when ^{1}H coupling was allowed is given in parentheses.

(16) Landauer, S. R.; Rydon, H. N. *J. Chem. Soc.* **1953**, 2224.

Lithiation of Polychloropyrimidines and Dichloropyridines

Rumen Radinov,*[1] Christo Chanev, and Marietta Haimova

Faculty of Chemistry, University of Sofia, 1 Anton Ivanov Avenue, Sofia 1126, Bulgaria

Received January 30, 1991

Lithiation of aromatic compounds is useful for synthesis of polyfunctional derivatives and heteropolycycles, and as π-deficient heterocycles the pyridines have attracted much attention. The ortho-directing efficiency of halogens in the reaction should be pointed out in particular.[2] Metalation of related pyrimidines is scarcely documented[3] with a few notable exceptions, viz. the recent regioselective lithiation of methoxypyrimidines with LTMP.[4] Under the same conditions, lithiation of 2,4-dichloropyrimidine (1a) was not regioselective as the two possible lithio derivatives were trapped in equal amounts and in low yield.[5]

We have disclosed the preparation of (α-hydroxybenzyl)pyridines and -pyrimidines via ortho-lithiation of

(1) Present address: Department of Organic Chemistry, University of Geneva, 30 quai Ernest-Ansermet, 1211 Geneva, Switzerland.

(2) (a) Trécourt, F.; Marsais, F.; Güngör, T; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409. (b) Marsais, F.; Trécourt, F.; Bréant, P.; Quéguiner, G. *J. Heterocycl. Chem.* **1988**, *25*, 81.

(3) (a) Kress, T. J. *J. Org. Chem.* **1979**, *44*, 2081. (b) Parkanyi, C.; Cho, N. S.; Yoo, G. S. *J. Organomet. Chem.* **1988**, *342*, 1.

(4) (a) Mattson, R. J.; Sloan, C. P. *J. Org. Chem.* **1990**, *55*, 3410. (b) Wada, A.; Yamamoto, J.; Hamaoka, Y.; Ohki, K.; Nagai, S.; Kanatomo, S. *J. Heterocycl. Chem.* **1990**, *27*, 1831.

(5) Turck, A.; Plé, N.; Mojovic, L.; Quéguiner, G. *J. Heterocycl. Chem.* **1990**, *27*, 1377.

0022-3263/91/1956-4793$02.50/0 © 1991 American Chemical Society