bromo-2-butene could be detected in the NMR of the distillate.

Treatment of *trans*-1,4-dibromo-2-butene with lithium amalgam afforded butadiene.

Acknowledgment. We thank the Chemistry Department of Washington University for allowing us the use of their JASCO Model J20 spectropolarimeter and the NSF and the University of Missouri-St. Louis for financial support.

Registry No. 2-Butyne-1,4-diol, 110-65-6; *cis*-2,3-dideuteriobutane-1,4-diol, 56543-04-5; *dl*-2,3-dibromo-2,3-dideuteriobutane-1,4-diol, 78019-68-8; *dl*-2,3-dibromo-2,3-dideuteriobutane-1,4-diol 1,4-dihemisuccinate, 78019-69-9; (2*R*,3*R*)-(+)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol, 78087-06-6; (2*S*,3*S*)-(−)-2,3-dibromo-2,3-dideuteriobutane-1,4-diol, 78087-07-7; (2*S*,3*S*)-(+)-dideuteriosuccinic acid, 78087-08-8; (2*R*,3*R*)-(−)-dideuteriosuccinic acid, 78087-09-9; (2*R*,3*R*)-dideuteriosuccinic anhydride, 78019-70-2; (2*S*,3*S*)-1,4-dibromo-2,3-dideuteriobutane, 78087-10-2; 1,2,4-tribromo-2,3-dideuteriobutane, 78019-71-3; (2*R*,3*R*)-1,4-dibromo-2,3-dideuteriobutane, 78087-11-3; butadiene-2,3-d_2, 1983-06-8; butane-2,3-d_2, 78019-72-4; (1*R*,2*R*)-1,2-dideuteriocyclobutane, 78087-12-4; (1*S*,2*S*)-dideuteriocyclobutane, 78087-13-5; 3-buten-1-ol, 627-27-0; 1,3,4-tribromobutane, 38300-67-3; *cis*-1,4-dibromo-2-butene, 18866-73-4; *trans*-1,4-dibromo-2-butene, 821-06-7; *cis*-2-butene-1,4-diol, 6117-80-2; *trans*-2-butene-1,4-diol, 821-11-4; butane-1,4-diol, 110-63-4; 1,4-dibromobutane, 110-52-1; 1,3-butadiene, 106-99-0; (*R*)-(−)-deuteriosuccinic acid, 3038-36-6; (*S*)-(+)-deuteriosuccinic acid, 10013-03-3.

New Synthesis of Azetidine

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Received April 20, 1981

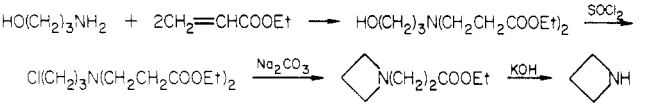
Unlike its smaller and larger homologues, azetidine is available commerically only in small quantities and is expensive.[1]

Although we were able to repeat the literature procedure[2] (Scheme I) and the reduction of tosylazetidine[3a] (Scheme II) on the scale described in the literature, we were unable to scale up either preparation significantly.

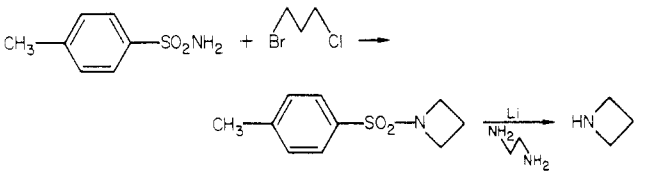
We report here a new synthesis which is convenient for the preparation of moderate quantities of azetidine. The procedure is shown in Scheme III.[4]

Reaction of acrolein with sodium azide in acetic acid[5] gave β-azidopropionaldehyde (1), which was reduced with sodium borohydride to 3-azidopropanol (2).[6] The very facile Staudinger reaction[7a] of 2 with triphenylphosphine in ether afforded the intermediate crystalline alcohol **3a** which on heating gave azetidine in 33% yield. The resulting azetidine contained some benzene, presumably as a result of a process involving a hydride (or proton) transfer

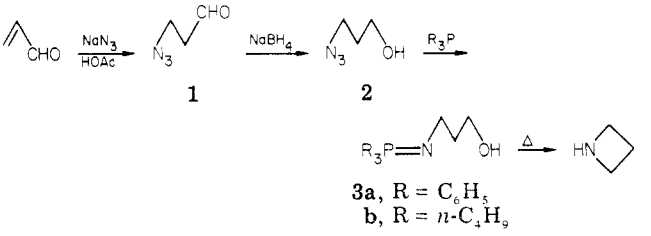
Scheme I. Azetidine Synthesis by the Literature Procedure[2]



Scheme II. Azetidine Synthesis by the Reduction of Tosylazetidine[3]

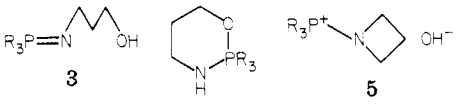


Scheme III



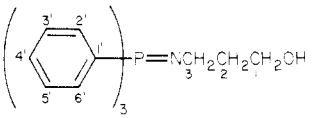
3a, R = C_6H_5
b, R = n-C_4H_9

Chart I



4a, R = C_6H_5
b, R = n-C_4H_9

Table I. NMR Data for 3a



^{1}H data		^{13}C data		
atom	shift, δ	atom	shift, δ	coupling const, Hz
H_1	3.94	C_1	65.42	J_{PNCCC} = 0
H_2	1.80	C_2	33.76	J_{PNCC} = 18.3
H_3	3.35	C_3	45.64	J_{PNC} = 6.1
$H_{2',6'}$	7.70	$C_{1'}$	132.80	J_{PC} = 6
$H_{3',4',5'}$	7.50	$C_{2',6'}$	132.20	J_{PCC} = 9.0
		$C_{3',5'}$	128.27	J_{PCCC} = 11.6
		$C_{4'}$	131.21	J_{PCCCC} = 2.7

Table II. NMR Data for 3b

$(CH_3CH_2CH_2CH_2)_3P{=}NCH_2CH_2CH_2OH$
4′ 3′ 2′ 1′ 3 2 1

^{1}H data		^{13}C data		
atom	shift, δ	atom	shift, δ	coupling const, Hz
H_1	3.84	C_1	67.70	J_{PNCCC} = 0
H_2	1.80	C_2	34.21	J_{PNCC} = 14.3
H_3	3.24	C_3	44.97	J_{PNC} = 3.0
$H_{1'}$	1.60	$C_{1'}$	27.85	J_{PC} = 65
$H_{2'}$	1.50	$C_{2'}$	24.22	J_{PCC} = 17.2
$H_{3'}$	1.40	$C_{3'}$	23.97	J_{PCCC} = 3.5
$H_{4'}$	0.96	$C_{4'}$	13.61	J_{PCCCC} ≈ 0

(1) See the Kodak Laboratory Chemicals catalog and the Tridom-Fluka catalog.
(2) Wadsworth, D. H. *Org. Synth.* **1973**, *53*, 13.
(3) (a) Gallegos, E. J.; Kiser, R. W. *J. Phys. Chem.* **1962**, *66*, 136. (b) For a review of this methodology see: Moore, J. A. In "Heterocyclic compounds with Three or Four-Membered Rings"; Weisberger, A., Ed.; Interscience: New York, **1964**; Chapter VII, p 898, trimethyleneimine. (c) Cf. also: White, J.; McGillivray, G. *J. Org. Chem.* **1974**, *39*, 1973.
(4) This process is similar to that reported for the synthesis of 2-phenylaziridine by: Blum, J.; et al. *J. Org. Chem.* **1978**, *43*, 4271.
(5) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5248.
(6) Hassner, A.; Galle, J. E. *J. Org. Chem.* **1976**, *47*, 2273.
(7) (a) Gololobov, Y. G.; Zhmurova, I. N.; Kasukhin, L. F. *Tetrahedron* **1981**, *37*, 437-472. (b) Another structural possibility is a pentacoordinate phosphorane $R_3P(OH)NCH_2CH_2CH_2$. Note the ionic structure proposed for the product of the reaction of 3-azidopropyl iodide with Ph_3P by Hassner and Galle;[6] in this case also a pentacoordinate phosphorane may be a possibility.

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and a phosphorus–carbon bond cleavage.

The structure of compound **3a** was established by X-ray methods and thus excluded structures **4a** and **5a** (shown in Chart I) from consideration. However, **4** and/or **5**[7b] could conceivably intervene as reaction intermediates during the heating of **3a** or **3b** to give azetidine.

We have carried out the analogous reaction with **2** and tri-*n*-butylphosphine and obtained **3b** as an oil which could be purified by distillation. Heating of distilled **3b** gave azetidine in 29% yield. If the crude oil was used, the resulting azetidine contained some ethanol.

The structure of **3b** was confirmed by comparison of the ^1H and ^{13}C NMR spectra with those of **3a** (see Tables I and II). Three points related to those spectra deserve comments. First, a comparison of the chemical shifts of **3b** to those of **3a** indicated strongly the structural similarity of the two compounds. Second, ^1H NMR and ^{13}C NMR rule out structure **5** as a possibility, since the signal pattern expected for the azetidine moiety is not observed in either spectrum. Third, while the ^1H NMR spectra of **3a** and **3b** do not distinguish structure **3** from **4**, the ^{13}C NMR spectra allow us to do that by correlation of the carbon–phosphorus coupling constants. In both samples the usual coupling P–N–C,P–N–C–C is observed, but the carbon bearing the hydroxyl group shows no coupling to the phosphorus atom. This eliminates structure **4**: in structure **4** a typical coupling constant would be expected between the carbinol carbon and the phosphorus atom since J_{POC} values are usually between 4.5 and 10.5 Hz.[8-10]

X-ray Study of 3a

Crystal data for **3a** ($C_{21}H_{22}NOP$) were as follows: triclinic, space group $P\bar{1}$, $Z = 4$, $a = 8.755$ (4) Å, $b = 10.771$ (2) Å, $c = 19.049$ (2) Å, $\alpha = 93.99$ (1)°, $\beta = 95.17$ (2)°, $\gamma = 92.05$ (1)°, $d_{measd} = 1.23$ g/cm^3, $D_{calcd} = 1.25$ g/cm^3, μ(Cu K) = 13.1 cm^{-1}, 5902 reflections (4956 reflections with intensities greater than1 standard deviation). Intensity data for all reflections with $2\theta < 138°$ were collected at low temperature (−155 °C) by using the step-scan technique[11] and graphite-monochromatized Cu K_α radiation (λ = 1.5418 Å) on a Syntex $P\bar{1}$ diffractometer controlled by a Harris computer.

There were two symmetry-independent molecules related by an approximate screw axis in the x direction at about 1/2 in y and 1/4 in z. Coordinates and anisotropic thermal parameters of nonhydrogen atoms were refined by multiple-matrix least-squares minimizing the function $\sum w(F_o^2 - F_c^2)^2$ where weights w were taken as the reciprocals of the variances $\sigma^2(F_o^2)$. Hydrogen parameters were included in the calculations but were not refined. Except for the hydroxyl hydrogens which were found in a difference Fourier map, the hydrogen coordinates were generated by using standard geometry. In both molecules there was an internal hydrogen bond between the hydroxyl and the nitrogen; the O–N distance was 2.72 Å for both. The final agreement index R, $[R = \sum||F_o| - |F_c||/\sum|F_o|]$, was 0.111, and the standard deviation of fit was 2.52.[12] All calculations were carried out on an IBM 370 computer with the CRYM system of crystallographic programs.[13,14]

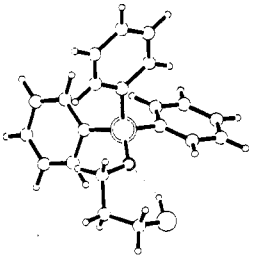

Figure 1. Computer drawing of compound **3a**.

A computer drawing of compound **3a** is shown in Figure 1.

Experimental Section

Melting points were taken in capillary tubes and are corrected. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer, IR spectra on a Perkin-Elmer Model 421 spectrophotometer, mass spectra at 70 eV on an Atlas Model CH-4 spectrometer, and NMR spectra on a Varian Model A-60A or XL-100 spectrometer. NMR peaks are recorded in parts per million downfield from tetramethylsilane.

3-Azidopropanol (2).[5,6] A solution of sodium azide (29.3 g, 0.461 mol, in 113 mL of H_2O) was added during 30 min to a solution of acrolein (17.2 g, 0.307 mol, in 45 mL of HOAc) with intermittent cooling (dry ice–acetone) to keep the temperature below 5 °C. Stirring was then continued for 30 min without cooling. The solution was extracted with ether (2 × 250 mL), the extract was washed with 100 mL of saturated Na_2CO_3 solution (**Caution**: foaming), dried ($MgSO_4$) and concentrated at room temperature to ca.250 mL. The ether solution was added during 30 min to a solution of $NaBH_4$ (5 g in 30 mL of H_2O) with cooling to keep the temperature below 20 °C. The mixture was stirred for 15 min and saturated with solid NaCl. The organic layer was dried ($MgSO_4$), evaporated, and kept 3 h in vacuo at 0.2 mm: 19.7 g (63% yield); NMR and IR were in accord.

3-[(Triphenylphosphoranylidene)amino]-1-propanol (3a). A mixture of the above azido alcohol **2** (5.05 g, 0.05 mol), triphenylphosphine (13.1 g, 0.05 mol), and 250 mL of ether was stirred overnight at room temperature. The initial solution turned to a suspension after ca.20 min. It was filtered and washed with ether to give 11.5 g of **3a** (67% yield). A sample was triturated with ether for analysis: mp 152–154 °C; UV (EtOH) 222 (26 850), 248 (sh, 692), 255 (sh, 1100), 259 (1550), 265 (2100), 272 (1800); IR 3130 (OH, br), 1588, 1573, 1483, 1481 (C=C), 1440, 1434 (PC_6H_5), 1208, 1193, 1114, 1109, 1071, 1010 (PPh/CO/CN), 722, 713, 698 (other); ^1H NMR and ^{13}C NMR spectra are discussed in the text; mass spectrum, (m/e) 335 (M^+). Anal. Calcd for $C_{21}H_{22}NOP$: C, 75.21; H, 6.61; N, 4.18; P, 9.23. Found: C, 75.43; H, 6.40; N, 3.90; P, 9.36.

Compound **3a** decomposed on standing at room temperature but could be kept in the cold.

Compound **3a** was crystallized from ether for X-ray analysis.

Preparation of Azetidine from 3a. The above alcohol **3a** (202 g) was placed in a 500-mL flask and heated in an oil bath at ~240 °C. The distillate (13.2 g) was collected by cooling with dry ice–acetone. An additional 202 g of **3a** was heated directly with a Bunsen burner, and 13.7 g of product was collected. NMR analysis of the total amount (26.9 g) showed azetidine and also 15% of benzene. The amount of azetidine present was therefore 22.9 g (33% yield). The mass spectrum showed benzene and azetidine (M^+, m/e 78 and 57).

3-[(Tri-*n*-butylphosphoranylidene)-1-propanol (3b). A solution of the azido alcohol **2** (5.05 g, 0.05 mol) in 25 mL of ether was added to a solution of tri-*n*-butylphosphine (10.1 g, 0.05 mol) in 200 mL of ether during 7 min. Mild reflux resulted, and stirring was continued for 18 h. The mixture was evaporated to give 13.4 g of product. Distillation of 6 g of this from an oil-jacket flask gave 4.53 g (74% yield) of an oil, bp 125–135 °C (0.2 mm). The

(8) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972.
(9) Levy, G. C.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists"; Wiley-Interscience: New York, 1972.
(10) Johnson, L. F.; Jankowski, W. C. "Carbon-13 Spectra"; Wiley: New York, 1972.
(11) Duchamp, D. J. *ACS Symp. Ser.* **1977**, *No. 46*, 98–121.
(12) Final atomic positional parameters have been deposited with the Crystallographic Data Centre, Cambridge, England. These coordinates may be accessed in the Cambridge Crystallographic Database by using the bibliographic reference to this paper.
(13) The CRYM system of crystallographic programs was written by: David J. Duchamp, The Upjohn Co., Kalamazoo, MI 49001.
(14) The authors thank the referees and Professor J. A. Moore for helpful comments.

following measurements were obtained on the freshly prepared sample: ^1H NMR and ^{13}C NMR spectra are discussed in the text; high-resolution mass spectrum. Calcd for $C_{15}H_{34}NOP$ m/e 275.2378, found m/e 275.2339.

On being allowed stand at room temperature, the product decomposed largely to tri-*n*-butylphosphine oxide.

Preparation of Azetidine from 3b. The above freshly distilled oil **3b** (4.53 g, 0.0164 mol) was heated at 190 °C for 1.5 h and the distallate collected by cooling in dry ice. The distillate (270 mg, 29% yield) was identified as azetidine by ^1H NMR and was shown to be 98% pure by GC and free of ethanol.

When the crude undistilled oil **3b** was used above, the final product, azetidine, contained some ethanol.

Registry No. 2, 72320-38-8; **3a**, 78064-88-7; **3b**, 78064-89-8; acrolein, 107-02-8; triphenylphosphine, 603-35-0; azetidine, 503-29-7; tri-*n*-butylphosphine, 998-40-3.

Supplementary Material Available: Tables of final crystallographic results on **3a**, consisting of atomic coordinates (also deposited with the Cambridge Data Base[12]), anisotropic thermal parameters, and generated hydrogen coordinates (3 pages). Ordering information is given on any current masthead page.

Regioselective Metalation of the 4-Position of Pyridine. New and Convenient Alkylation and Acylation of 3-Amino-5-methoxypyridine

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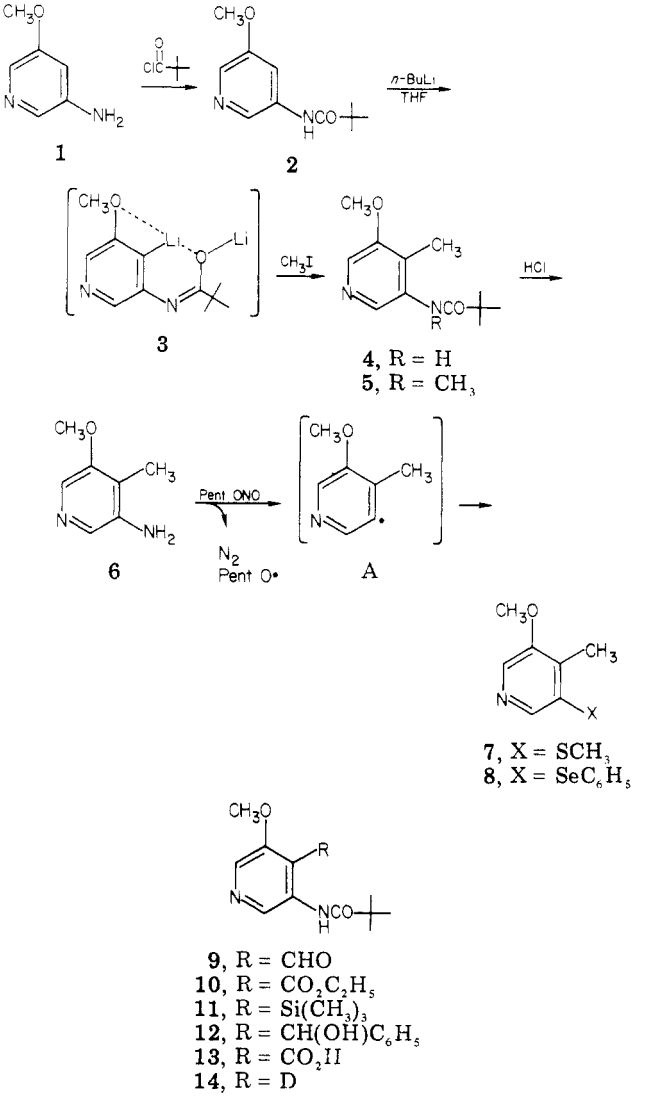
Prior to the work of Meyers[1,2] using the oxazoline functionality as an activating group, the direct metalation of pyridine was limited to a few examples.[3,4] The Meyers method gives a regioselective metalation of the 3-position of 4-(4,4-dimethyloxazolinyl-2-yl)pyridine by methyllithium and the 4-position of 3-(4,4-dimethyloxazolinyl-2-yl)pyridine by lithium amide. Very recently, regioselective lithiation of ethyl esters of nicotinic and isonicotinic acids,[5] halopyridines,[6] and *N,N*-diisopropylpyridylcarboxylic amides by lithium amide has been reported.[7] These results prompted us to publish our own results on the regioselective and direct ortho lithiation of 3-methoxy-5-(pivaloylamino)pyridine by *n*-butyllithium which affords 4-functionalized pyridine derivatives. Thus, 3-amino-5-methoxypyridine (**1**), readily obtained by a three-step sequence starting with 3,5-dibromopyridine *N*-oxide,[8] was transformed into the *N*-pivaloyl derivative (**2**) and was reacted with an excess of *n*-butyllithium to give the 4-lithio derivative (**3**). 3-Methoxy-5-(pivaloylamino)-4-methylpyridine (**4**) was isolated from the reaction mixture by quenching with methyl iodide. Optimization of the reaction conditions for the formation of **4** showed that the best yield (99% overall yield from **2**) was obtained when metalation was performed with 2.5 equiv of *n*-butyllithium at −25 °C for 1 h and the formed lithio derivative (**3**) was quenched with 4 equiv of methyl iodide at −70 °C. No 3-methoxy-4-methyl-5-(*N*-methylpivaloylamino)pyridine (**5**) was formed, although this substance could be prepared when the reaction was quenched with 4 equiv of methyl iodide at 0 °C. The combined activating effect toward alkyllithium by both *N*-pivaloylamino and methoxy groups ("coordination only" mechanism)[9] is

Scheme I



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(3) The organolithium reagents usually add across the C=N bond of pyridines: Wakefield, B. J., "The Chemistry of Organolithium Compounds"; Pergamon Press: Elmsford, NY, 1974; pp 112–116. Therefore, lithiated pyridines have been obtained by halogen–metal exchange reactions of bromopyridines: Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485; Wibaut, J. P. de Jonge, A. P.; van der Voort, H. G. P.; Otto, P. Ph. H. L. *Recl. Trav. Chim. Pays-Bas* **1951**, *70*, 1054; Murray, A., III; Foreman, W. W.; Langham, W. *J. Am. Chem. Soc.* **1948**, *70*, 1037; Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257.
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(6) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.
(7) Epsztajn, J.; Berski, Z.; Brzeziński, J. Z.; Jóźwiak, A. *Tetrahedron Lett.* **1980**, *21*, 4739.
(8) A facile preparation of the starting compound (**1**) is as follows. Refluxing a methanolic solution of 3,5-dibromopyridine *N*-oxide and KOH for 30 min gave a 79% yield of 3-bromo-5-methoxypyridine *N*-oxide [mp 200–210 °C (recrystallized from methanol); ν_{max} 1580, 1550, 1410 cm^{-1}], which was converted to 3-amino-5-methoxypyridine *N*-oxide [syrup; 95%; ν_{max} 1640, 1605, 1565, 1210 cm^{-1}; m/e 140 (M^+)] by treatment with aqueous ammonia–$CuSO_4$ in a sealed tube at 130 °C for 5 h. Deoxygenation of the oxide by the catalytic hydrogenation on Raney Ni in methanol at room temperature for 1 h gave a 95% yield of **1** [mp 54–55 °C (recrystallized from benzene); bp 185 °C (18 mmHg) [lit.[12] bp 166–168 °C (15 mmHg)]]; see: Tamura, Y.; Fujita, M.; Chen, L. C.; Kiyokawa, H.; Ueno, K.; Kita, Y. *Heterocycles* **1981**, *15*, 871.
(9) For a review of ortho lithiations, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–360; Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133; Marburg, S.; Tolman, R. L. *J. Heterocycl. Chem.* **1980**, *17*, 1333.

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