The present method has several advantages over those of Takahashi,[5] Austin,[7] and Herbenrother[8,15] because (1) MEBYNOL is used as a coupling agent instead of trimethylsilyl acetylene, (2) much higher overall yields of EBA and EBC are obtained, 97% instead of 59%[15] and 96% instead of 39%,[15], respectively, and (3) the overall reaction time was reduced from 14 h to 50 min.[15]

Experimental Section

General Methods. Melting points are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 200 MHz. Chemical shifts (δ) are given in parts per million, with tetramethylsilane as internal standard. HPLC was run using a UV detector (254 nm) with methanol as the eluting solvent. GPC was run on a Waters GPC I equipped with a differential refractomonitor and a UV detector using two Plgel columns (5 μm, 10 and 500 Å), with THF as the eluant.

Starting Materials. All reagents were used as received except pyridine and triethylamine which were refluxed over KOH pellets overnight and distilled just before use. Methyl *p*-bromobenzoate was prepared quantitatively by refluxing *p*-bromobenzoic acid (200 g) with an excess of methanol (400 g) and a catalytic amount of sulfuric acid (12 g) (purity: 99.7% by HPLC and GPC).

4-(4-(Methoxycarbonyl)phenyl)-2-methyl-3-butyn-2-ol (1). Dichlorobis(triphenylphosphine)palladium (0.48 g, 0.68 mmol) was added under N_2 to a solution of Ph_3P (1.74 g, 6.6 mmol), CuI (0.46 g, 2.4 mmol), methyl *p*-bromobenzoate (124.6 g, 580 mmol), and MEBYNOL (58 g, 690 mmol) in 800 mL of dry Et_3N and 320 mL of dry pyridine and refluxed under N_2 for 40 min. The mixture was cooled to rt and filtered to remove the insoluble triethylamine hydrobromide. The salt was washed with triethylamine and ethyl ether until the ether washings were clear. The combined filtrates were reduced to dryness under reduced pressure. The obtained solid was stirred twice with H_2O and then with 1 L of 3% HCl and again twice with H_2O. The mixture was filtered, and the residue was dried under vacuum to yield 1, light tan color (123.82 g, 98% yield), mp 84–85 °C (lit.[12] mp 83.5–84 °C, lit.[3] mp 83.5–84 °C) and 99% purity (by HPLC and GPC). Compound 1 was recrystallized from a small volume of toluene to give off-white crystals (99.7% purity by HPLC and GPC).

***p*-Ethynylbenzoic Acid (2).** Sixty-six g (1.65 mol) of sodium hydroxide were dissolved in refluxing 1-butanol (2.6L); 90 g (0.41 mol) of 1 were added at once, and the mixture was refluxed for 10 min. After being cooled in an ice-bath and filtered, the white residue was stirred with refluxing 2-propanol (600 mL) twice and dried at 60 °C under vacuum to give the sodium salt of EBA (98.5% yield, 99% purity by analyzing the free acid by GPC). IR (KBr pellet, cm^{-1}): 3298 (C–H stretching of ethynyl); 2106 (weak band, C–C stretching of ethynyl); 1585 (asymmetric stretching of carboxylate anion); 1543 (C–C stretching of aromatic); 1390 (symmetric stretching of carboxylate anion); 621 (aromatic C–H deformation).

The hydrolysis–deprotection reaction was complete after 2 h at reflux using KOH (4 equiv), 5% w/v in 2-propanol.

p-Ethynylbenzoic acid was obtained by acidifying the salt solution to pH 2.5. It was obtained quantitatively as a white solid in 97% overall yield (lit.[15] yield 59%) with 99% purity (by GPC) and mp 224–225 °C (lit.[1] mp 218 °C dec, lit.[2] mp 215–220 °C dec, lit.[8] mp 222–223 °C dec, lit.[15] mp 220–223 °C dec).

EBA salts are stable as solids and in solution. Upon acidification the acid precipitates; it changes color even at room temperature and while being dried under vacuum. Freshly synthesized, undried EBA can be stored without polymerization at −15 °C. It is noteworthy that the corresponding potassium or sodium salts are stable toward drying at 60 °C under vacuum and storage for extended periods at room temperature.

***p*-Ethynyl Benzoyl Chloride.** The potassium salt of EBA (94.0 g) in 300 mL of $CHCl_3$ was stirred at 0 °C, while $SOCl_2$ (140 mL) was added gradually. The reaction was exothermic. One mL of DMF was then added, and the mixture was stirred at rt for 5 h. The resulting orange solution was evaporated under vacuum to dryness at about 40 °C. The yellow residue was stirred sequentially with three 400-mL portions of ethyl ether for 30 min, and the combined filtrates were evaporated to dryness. A yellow crystalline product was obtained (83.3g), 99% yield, 96% overall yield from methyl *p*-bromobenzoate (lit.[15] yield 39%)), mp 78–79 °C (lit.[8] mp 68–69 °C, lit.[15] mp 74.5–76 °C, lit.[17] 76–77 °C and 99% purity (HPLC). ^{1}H-NMR (acetone-d_6): δ 8.12 (d, 2 H, J = 8.5 Hz, aromatic ortho to –COCl); 7.70 (d, 2 H, J = 8.5 Hz aromatic ortho to ethynyl group); 4.04 (s, 1 H, ethynyl group). FTIR (KBr pellet, cm^{-1}): 3267 (C–H stretching of ethynyl); 2106 (C–C stretching of ethynyl); 1776 (carbonyl stretching); 1730 (carbonyl stretching); 1689, 1588 (C–C stretching of aromatic ring); 1203 (C–H out of plane bending of aromatic ring). It should be noted that the absence of a band at 3550–3300 cm^{-1} confirmed that EBC does not contain even traces of EBA. EBC was recrystallized from petroleum ether, hexanes, or a small volume of ethyl ether.

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Metalation–Alkylation of *O*-Trimethylsilyl Formyltrimethylsilane Cyanohydrin in the Synthesis of Oxazoles

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We have recently shown[1,2] that *O*-trimethylsilyl acylsilane cyanohydrins 1 may be employed for the formation of oxazoles (Scheme I). Even though both acylsilanes (after TMSCN addition) and aldehydes (upon metalation–silylation of their *O*-trimethylsilyl cyanohydrins) have served as precursors to 1, the methodology would exhibit wider scope if 1 were accessible through R^1X alkylation of the carbanion derived from the metalation of 4 (Scheme II). Although 4 was readily available, our earlier observation[3] that 4 could not be metalated by LDA seemed to preclude this approach. We now report that the less-hindered metal amides lithium dimethylamide and lithium diethylamide (LDEA) metalate 4 even at −95 °C.

To illustrate the utility of this approach, 4 was metalated with LDEA, followed by alkylation with a sampling of alkyl halides. The results (Table I) indicate that high yields of **1a–1e** are obtained using either primary or secondary alkyl iodides (*tert*-butyl iodide gave no product[4]) or reactive alkyl bromides (benzyl chloride afforded a complex mixture of products). These species were then treated sequentially in the manner depicted by Scheme I to first afford **2a–2e**[5] which could then be converted without purification into the corresponding oxazoles **3a–3e** in good overall yields (Table I). In particular, we note that this

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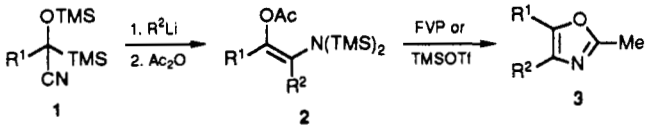
(4) Interestingly, the carbanion derived from *O*-TMS benzaldehyde cyanohydrin affords a high yield of alkylated product with *tert*-butyl iodide: Deuchert, K.; Hertenstein, U.; Hünig, S.; Wehner, G. *Chem. Ber.* **1979**, *112*, 2045.
(5) Each 2 was monoisomeric and assumed to be of *Z* stereochemistry based solely on analogy to similarly prepared *O*-TMS systems: Cunico, R. F.; Kuan, C. P. *J. Org. Chem.* **1990**, *55*, 4634.

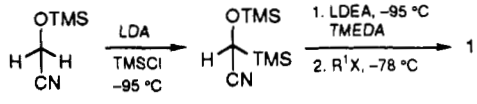
0022-3263/92/1957-6999$03.00/0

Scheme I



1 2 3

Scheme II



4

approach suggests easy access to bulky substituents at the C-5 oxazole position via similarly substituted 1, a goal which was difficult to achieve by our earlier route.[2]

Experimental Section

NMR spectra were obtained at 200 MHz in $CDCl_3$. IR spectra were of neat films. Preparative and analytical GLC utilized a 2-ft × 0.25-in. 20% SE-30 column. Oven temperatures (Kd) are listed for Kugelrohr distillations. All reactions were carried out under positive argon pressure. THF was distilled from sodium benzophenone ketyl immediately before use. An acetone–liquid N_2 slush bath contained in a Dewar flask was used for reactions carried out at −95 °C. The term "anhydrous workup" indicates that the reaction mixture was evacuated at 1 mmHg (25 °C), pentane added to the residue, the mixture filtered through a glass frit under Ar, and solvent removed under vacuum. *n*-Butyllithium in hexane (nBuLi) and methyllithium in ether (MeLi) were obtained from Aldrich Chemical Co.

2-(Trimethylsilyl)-2-[(trimethylsilyl)oxy]ethanenitrile (4).[3] The following procedure is more convenient for large-scale preparations than the original. LDA was prepared at −78 °C from nBuLi (2.35 M, 33 mL, 78 mmol) and diisopropylamine (7.8 g, 78 mmol) in 90 mL of THF. After 30 min, TMSCl (8.6 g, 79 mmol) was added dropwise, and the mixture was cooled to −95 °C. A precooled (−78 °C) solution of 2-[(trimethylsilyl)oxy]ethanenitrile[3] (10 g, 78 mmol) in 20 mL of THF was then added, and the mixture was allowed to slowly warm to 25 °C and was stirred overnight. The yellow solution was treated with 3–4-drop increments of methanol until no further lightening of the pale yellow color occurred. After an anhydrous workup, short-path distillation gave 12.1 g (77%) of 4, bp 50–51 °C (1 mm).

2-(Trimethylsilyl)-2-[(trimethylsilyl)oxy]hexanenitrile (1a). This procedure is representative of all preparations of 1. A mixture of diethylamine (0.56 g, 7.7 mmol) and TMEDA (0.89 g, 7.7 mmol) in 25 mL of THF at −78 °C was treated with nBuLi (2.5M, 3.1 mL, 7.7 mmol). After 30 min, ether (10 mL) was added and the mixture was cooled to −95 °C. A solution of 4 (1.4 g, 7.0 mmol) in 10 mL of THF precooled to −78 °C was then added dropwise, followed by substitution of dry ice for liquid N_2 in the cooling bath. After 1.5 h at this temperature, 1-iodobutane (1.42 g, 7.7 mmol) in 10 mL of THF precooled to −78 °C was added, and the reaction mixture was allowed to warm to 25 °C. Pentane was added, and the organic phase was washed twice with water and then with saturated NaCl solution. The dried ($MgSO_4$) concentrate was short-path distilled to give 1.72 g of material, by 80–90 °C (3 mm), which GLC (130 °C) indicated was over 95% pure (91% yield): IR 2230 (w), 1255 (s), cm^{-1}; ^1H NMR δ 0.14 (s, 9 H), 0.19 (s, 9 H), 0.91 (t, J = 7 Hz, 3 H), 1.25–1.55 (m, 4 H), 1.65–1.75 (m, 2 H); ^{13}C NMR δ −4.0, 1.6, 13.9, 22.8, 27.2, 37.2, 65.4, 122.2. Anal. Calcd for $C_{12}H_{27}NOSi_2$: C, 55.97; H, 10.57; N, 5.44. Found: C, 55.75; H, 10.66; N, 5.39.

2,3-Bis(trimethylsilyl)-2-[(trimethylsilyl)oxy]propanenitrile (1b): bp 68–78 °C (0.01 mm); IR 2200 (w), 1255 (s) cm^{-1}; ^1H NMR δ 0.13 (s, 9 H), 0.17 (s, 9 H), 0.21 (s, 9 H), 1.17 (AB pattern, J = 15 Hz, 2 H); ^{13}C NMR δ −3.7, 0.1, 2.0, 27.3, 63.4, 123.1. Anal. Calcd for $C_{12}H_{29}NOSi_3$: C, 50.11; H, 10.16; N, 4.87. Found: C, 49.93; H, 10.39; N, 4.70.

3-Methyl-2-(trimethylsilyl)-2-[(trimethylsilyl)oxy]butanenitrile (1c):[3] bp 55–60 °C (1 mm).

Table I. Synthesis of 1–3

R^1X	1 (% yield)	2 (R^2)	3 (% yield)
nBuI	1a (91)	2a (nBu)	3a (80)
$TMSCH_2I$	1b (74)	2b (Me)	3b (70)
iPrI	1c (82)	2c (Me)	3c (72)
AllylBr	1d (97)	2d (nBu)	3d (73)
$PhCH_2Br$	1e (87)	2e (Me)	3e (72)

2-(Trimethylsilyl)-2-[(trimethylsilyl)oxy]-4-pentenenitrile (1d): Kd 75–80 °C (5 mm); IR 2200 (w), 1640 (w), 1252 (s) cm^{-1}; ^1H NMR δ 0.15 (s, 9 H), 0.19 (s, 9 H), 2.49 (d, J = 7 Hz, 2 H), 5.1–5.25 (m, 2 H), 5.75–6.0 (m, 1 H). ^{13}C NMR δ −4.0, 1.6, 41.9, 65.0, 119.4, 121.6, 132.4. Anal. Calcd for $C_{11}H_{23}NOSi_2$: C, 54.71; H, 9.60; N, 5.80. Found: C, 54.91; H, 9.90; N, 5.94.

3-Phenyl-2-(trimethylsilyl)-2-[(trimethylsilyl)oxy]propanenitrile (1e): bp 89–108 °C (0.05 mm) (lit.[3] Kd 98–140 °C (0.1 mm)).

2-[Bis(trimethylsilyl)amino]-3-(ethanoyloxy)-5-decene (2a). This procedure is representative of all preparations of 2. A solution of 1a (1.72 g, 6.34 mmol) in 50 mL of ether at 0 °C was treated with nBuLi (2.5M, 2.8 mL, 7.0 mmol) and was stirred 1 h at 25 °C. The solution was recooled to 0 °C, acetic anhydride (0.72 g, 7.0 mmol) was added, and stirring was continued for 1 h. After an anhydrous workup, the crude 2a was used directly for the synthesis of 3a. Spectral and analytical data on 2a were obtained from a sample isolated by preparative GLC (130 °C: IR 1740 (s), 1664 (w) cm^{-1}; ^1H NMR δ 0.10 (s, 18 H), 0.90 (m, 6 H), 1.33 (m, 8 H), 2.04 (m, 2 H), 2.10 (s, 3 H), 2.26 (m, 2 H); ^{13}C NMR δ 2.6, 13.86, 13.93, 21.5, 22.7, 23.2, 29.6, 29.8, 30.0, 34.8, 132.8, 141.1, 168.8. Anal. Calcd for $C_{18}H_{39}NO_2Si_2$: C, 60.44; H, 10.99; N, 3.92. Found: C, 60.28; H, 11.06; N, 4.17.

2-(Ethanoyloxy)-1-(trimethylsilyl)-3-[bis(trimethylsilyl)amino]-2-butene (2b): IR 1761 (s) cm^{-1}; ^1H NMR δ 0.04 (s, 9 H), 0.09 (s, 18 H), 1.67 (s, 3 H), 1.77 (s, 2 H), 2.05 (s, 3 H); ^{13}C NMR δ −0.8, 2.4, 20.2, 21.4, 22.9, 125.7, 140.5, 168.6. Anal. Calcd. for $C_{15}H_{35}NO_2Si_3$: C, 52.12; H, 10.20; N, 4.05. Found: C, 52.35; H, 10.39; N, 4.34.

3-(Ethanoyloxy)-4-methyl-2-[bis(trimethylsilyl)amino]-2-pentene (2c).[2]

4-(Ethanoyloxy)-5-[bis(trimethylsilyl)amino]-1,4-nonadiene (2d): IR 1760 (s), 1664 (w), 1635 (w) cm^{-1}; ^1H NMR δ 0.10 (s, 18 H), 0.90 (m, 3 H), 1.33 (m, 4 H), 2.05 (m, 2 H), 2.07 (s, 3 H), 3.04 (d, J = 7 Hz, 2 H), 5.0 (m, 2 H), 5.7 (m, 1 H); ^{13}C NMR (C_6D_6) δ 3.4, 14.5, 21.5, 23.9, 30.5, 35.70, 35.74, 116.9, 134.5, 135.8, 139.8, 168.4. Anal. Calcd for $C_{17}H_{35}NO_2Si_2$: C, 59.77; H, 10.33; N, 4.10. Found: C, 59.89; H, 10.45; N, 4.32.

2-(Ethanoyloxy)-1-phenyl-3-[bis(trimethylsilyl)amino]-2-butene (2e): IR 1735 (s) cm^{-1}; ^1H NMR δ 0.07 (s, 18 H), 1.84 (s, 3 H), 1.97 (s, 3 H), 3.66 (s, 2 H), 7.1–7.3 (m, 5 H); ^{13}C NMR δ 2.3, 21.1, 22.9, 35.9, 126.2, 128.2, 129.9, 138.4, 140.6, 168.9. Anal. Calcd for $C_{18}H_{31}NO_2Si_2$: C, 61.84; H, 8.94; N, 4.01. Found: C, 62.07; H, 9.03; N, 4.27.

4,5-Dibutyl-2-methyloxazole (3a). All oxazoles were prepared in this manner. The crude 2a obtained above was volatilized with air-bath heating into a 14-in. × 0.25-in. quartz Vigreux tube held at 600 °C under 1 mmHg vacuum. The pyrolysate was condensed at −78 °C and then distilled to give 1.10 g of 3a, 64–68 °C (0.5 mm) which GLC (110 °C) indicated was 90% pure (yield: 80%): IR 1640 (w), 1586 (s) cm^{-1}; ^1H NMR δ 0.85 (t, J = 7 Hz, 6 H), 1.28 (m, 4 H), 1.51 (m, 4 H), 2.29 (t, J = 7 Hz, 2 H), 2.30 (s, 3 H), 2.46 (t, J = 7 Hz, 2 H); ^{13}C NMR (C_6D_6) δ 14.2, 14.4, 14.6, 22.9, 23.1, 25.0, 26.2, 31.5, 32.2, 135.7, 146.9, 159.1. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.94; H, 10.83; N, 7.28.

2,4-Dimethyl-5-[(trimethylsilyl)methyl]oxazole (3b): bp 51–55 °C (0.5 mm); IR 1640 (m), 1586 (s) cm^{-1}; ^1H NMR δ 0.01 (s, 9 H), 1.88 (s, 2 H), 1.96 (s, 3 H), 2.3 (s, 3 H); ^{13}C NMR δ −1.5, 11.2, 13.8, 14.5, 127.9, 145.2, 157.8. Anal. Calcd for $C_9H_{17}OSi$: C, 58.97; H, 9.35; N, 7.64. Found: C, 58.77; H, 9.58; N, 7.77.

2,4-Dimethyl-5-(1-methylethyl)oxazole (3c):[2] bp 60–70 °C (20 mm).

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