An Easy and Useful Preparation of Propynyllithium from (Z/E)-1-Bromopropene

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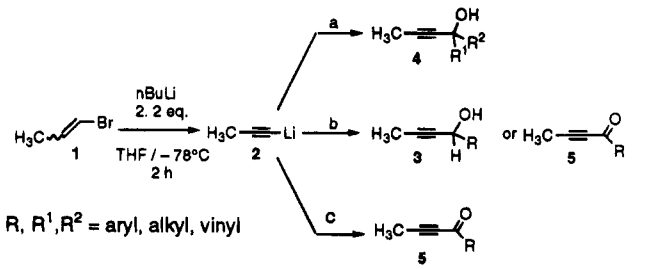
Received January 24, 1995

There are many reports in the literature on the reaction of metal acetylides with organic compounds in aprotic solvent,[1] but there are no reports on easy preparations of propynyllithium from commercially available compounds. In almost all cases propynyllithium or propynylsodium are prepared from the corresponding metal and propyne gas in liquid ammonia or other solvents,[2] by direct metalation with butyllithium[3] and by reaction of sodium hydride or lithium hydride in dimethyl sulfoxide with subsequent addition of propyne.[4] In only one report,[5] propynyllithium was prepared by direct metalation of allene with nBuLi at −78 °C. Since propyne is very expensive, in some cases it has been replaced by the cheap welding gas mixture MAPP (methylacetylene, propadiene, propene) which contains up to 13.5% of propyne.[6]

A study[7] of the addition of propynyllithium and propynylsodium to several electrophiles (e.g. aldehydes, ketones, halides) showed varying results. The reaction conditions, usually 20–90 °C, gave secondary and tertiary propargylic alcohols in yields which ranged from 5 to 91%. These conditions are usually incompatible with sensitive organic substrates. Propynyllithium has also been generated by the reaction of 1-chloropropene with n- or *sec*-BuLi.[8] Unfortunately its reaction with methyl iodide gave at best a 50% yield of product.

Scheme 1[a]



[a] (a) (1) $CeCl_3$, −78 °C, 1 h; (2) ketone, 1 h, −78 °C → 20 °C; (3) aqueous saturated NH_4Cl; (b) (1) aldehyde or Weinreb amide, 1 h, −78 °C → 20 °C; (2) aqueous saturated NH_4Cl; (c) (1) $ZnCl_2$, −20 °C, 15 min; (2) $Pd(PPh_3)_4$, 5 mol %, acid chloride, 0 °C, 30 min; (2) aqueous saturated NH_4Cl.

Since propynyllithium is widely used in the synthesis of natural and unnatural products,[6,9] it is of great importance to find a method for the easy generation of this species from simple, inexpensive commercially available starting material.

Herein, we report that propynyllithium **2** can be generated in anhydrous THF in high yield by reaction at −78 °C of the commercially available mixture of (*Z*/*E*)-1-bromopropene (**1**) with nBuLi (Scheme 1).

The results obtained are summarized in Table 1. The lithiated anion **2** reacted directly with aldehydes or Weinreb amides[10] to give the corresponding alcohols **3** or ketones **5** (entries 1–3 and 10–11, Table 1) or, after treatment with anhydrous $CeCl_3$, with ketones[11] to yield the tertiary propargylic alcohols **4** (entries 4–9, Table 1). Reaction of **2** with 1.1 equivalent of anhydrous $ZnCl_2$ in THF gave the transmetalated zincate[12] which in the presence of $Pd(PPh_3)_4$ reacted smoothly with acid chlorides to give ketones **5** in good yields (entries 12 and 13, Table 1).

As a model we chose the reaction between benzaldehyde and propynyllithium generated under various conditions (Scheme 2). Solvent, time, temperature, molar ratio, and the base used were found to be critical factors in obtaining good yields of adducts.

If nBuLi (entry 1, Table 2) was reacted for 30 min at 20 °C with (*Z*/*E*)-1-bromopropene and then treated with benzaldehyde for 1 h at −78 °C, a mixture of the corresponding propargylic alcohol **3a** and the diol **7** in a ratio 49:51 was obtained. When the anion was generated

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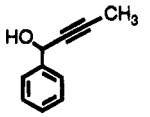
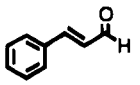
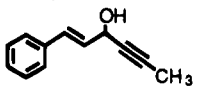
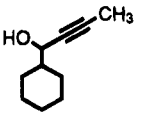
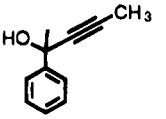
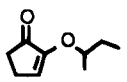
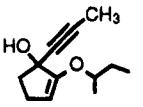
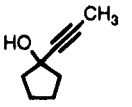
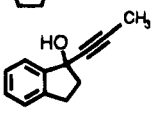
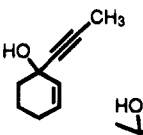
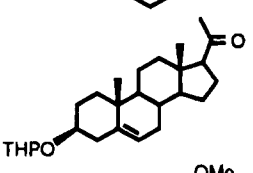
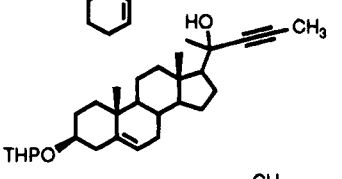
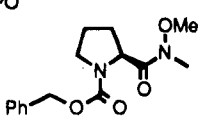
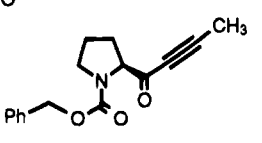
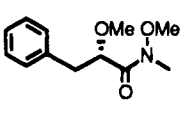
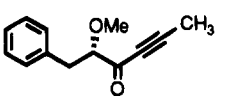
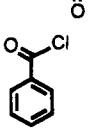
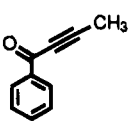
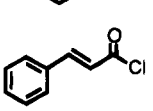
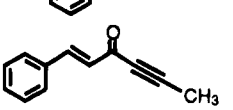
Table 1. Addition of 1-Propynyl Metal to Various Electrophiles

entry	starting compound	method	product	yield (%)
1		a	**3a** 	94
2		a	**3b** 	94
3		a	**3c** 	95
4		b	**4a** 	92
5		b	**4b** 	89
6		b	**4c** 	90
7		b	**4d** 	95
8		b	**4e** 	88
9		b	**4f** 	86
10		a	**5a** 	86
11		a	**5b** 	89
12		c	**5c** 	90
13		c	**5d** 	78

in THF at 0 °C and then warmed to 20 °C for 1 h (entry 2, Table 2) we isolated a 57:43 mixture of propargylic alcohol **3a** and diol **7** (Scheme 2). When **1** and nBuLi were reacted for only 30 min at −20 °C or −78 °C (entries 3 and 4, Table 2) we isolated a mixture of the expected product **3a** and **6**, resulting from addition of nBuLi to the electrophile in 42:58 and 60:40 ratios (see Table 2), respectively. By adjusting the molar ratio of the reagents from 1.2:1:2.2 of 1-bromopropene:benzaldehyde:nBuLi to 1.55:1:2.2 (entry 5, Table 2), at −78 °C for 2 h, we obtained adduct **3a** as the sole product. Interestingly the reaction in Et_2O (entry 6, Table 2) gave only **6** in 92% yield. No addition of propynyllithium was observed in this case.

With the use of *sec*-BuLi or tBuLi (entries 7 and 8, Table 2) instead of nBuLi (entry 5), only **3a** and **8** were isolated in both cases in ratios of 58:42 and 72:28, respectively. The allylic alcohol **8** resulted from the addition of (*E*)- and (*Z*)-1-propenyllithium to benzaldehyde (*E*/*Z* ratio not determined).

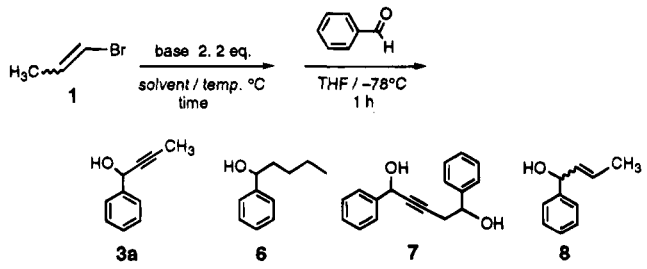
In conclusion, we have shown that propynyllithium can be easily generated from cheap and commercially avail-

Table 2. Study of the Interaction of 1 and Bases in the Formation of Propynyllithium

entry	molar ratio 1/PhCHO/base	base	t, °C[a]	time[b]	solvent	ratio[c] 3a (%)	6 (%)	7 (%)	8 (%)
1	1.2:1:2.2	nBuLi	20	30 min	THF	49	–	51	–
2	1.2:1:2.2	nBuLi	0 → 20	1 h	THF	57	–	43	–
3	1.2:1:2.2	nBuLi	−20	30 min	THF	42	58	–	–
4	1.2:1:2.2	nBuLi	−78	30 min	THF	60	40	–	–
5	1.55:1:2.2	nBuLi	−78	2 h	THF	100	–	–	–
6	1.55:1:2.2	nBuLi	−78	2 h	Et_2O	–	100	–	–
7	1.55:1:2.2	sBuLi[d]	−78	2 h	THF	58	–	–	42
8	1.55:1:2.2	tBuLi[d]	−78	2 h	THF	72	–	–	28

[a] Reaction temperature for the interaction of the base and (*Z*/*E*)-1-bromopropene; in all cases benzaldehyde was added at −78 °C and held at this temperature for 1 h. [b] Reaction time for the interaction of the base and (*Z*/*E*)-1-bromopropene. [c] Determined by ^1H NMR. [d] No addition of *sec*-BuLi or tBuLi on the aldehyde was observed.

Scheme 2



able (*E*/*Z*)-1-bromopropene, and that it reacts in high yield with aldehydes, ketones, amides, or acid chlorides to give the corresponding propargylic alcohols or ketones, respectively.

Experimental Section

For general experimental informations see reference 13.

Preparation of Propynyllithium and Addition to Electrophiles. General Procedures. Addition to Aldehydes and Weinreb Amides: Method a. A stirred solution of (*Z*/*E*)-1-bromopropene (Aldrich Chemical Co.; bp 58−63 °C/760 mmHg) (15.5 mmol, 1.87 g) in dry THF (10 mL) under argon at −78 °C was treated dropwise with a 1.55 M solution of nBuLi in hexane (22 mmol) over 10 min. The resulting milky mixture was stirred at −78 °C for an additional 2 h before a solution of the aldehyde or the Weinreb amide (10 mmol) in THF (5 mL) was slowly added at −78 °C. The reaction mixture was stirred for an additional 1 h at −78 °C before being allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added, and the product was extracted with Et_2O (3 × 30 mL). The organic layer was washed with brine (2 × 50 mL) and dried over Na_2SO_4. After filtration, the ether layer was concentrated *in vacuo*. Flash chromatography using the Still procedure (SiO_2, Et_2O−hexane) afforded the pure propargylic alcohol in high yield.

1-Phenyl-2-butyn-1-ol (3a): chromatography solvent Et_2O/hexane, 20:80, R_f 0.22, yield 94%; colorless oil; IR (cm^{-1}, $CHCl_3$) 3593, 3430, 3020, 2923, 2230; MS (EI, 70eV) 146 (100), 127 (62), 115 (88); ^1H NMR ($CDCl_3$) δ 1.92 (d, 3H, ^4J = 2.2 Hz), 2.30 (bd, 1H, ^3J = 5 Hz), 5.43 (bs, 1H), 7.32−7.44 (m, 3H), 7.51−7.57 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 3.35, 64.14, 79.13, 82.51, 126.32, 127.72, 128.13, 141.02. Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.77; H, 7.14.

6-Phenyl-hex-2-yn-5-en-4-ol (3b): chromatography solvent Et_2O/hexane, 20:80, R_f 0.25, yield 94%, colorless oil; IR (cm^{-1}, $CHCl_3$) 3596, 3430, 3020, 2239, 1630; MS (EI, 70 eV) 172 (19), 171 (13), 156 (39), 128 (76) 104 (100); ^1H NMR ($CDCl_3$) δ 1.91 (d, 3H, ^4J = 2.2 Hz), 2.45 (d, 1H, ^3J = 6 Hz), 5.04 (m, 1H), 6.31 (dd, 1H, ^3J = 16 Hz, ^3J = 6 Hz), 6.75 (dd, 1H, ^3J = 16 Hz, ^4J = 0.7 Hz), 7.23−7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 2.97, 62.34, 75.71, 82.14, 125.99, 127.21, 127.81, 127.97, 130.66, 135.40. Anal. Calcd for $C_{12}H_{12}O$: C, 83.64; H, 7.02. Found: C, 83.01; H, 6.96.

1-Cyclohexyl-2-butyn-1-ol (3c): chromatography solvent Et_2O/hexane, 20:80, R_f 0.25, yield 95%, colorless oil; IR (cm^{-1}, $CHCl_3$) 3609, 3437, 2931, 2855; MS (EI, 70eV) 152 (2), 137 (38), 123 (20), 109 (23); ^1H NMR ($CDCl_3$) δ 0.99−1.41 (m, 6H), 1.42−1.58 (m, 1H), 1.65−1.90 (m, 9H), 1.85 (d, 3H, ^3J = 2.2 Hz), 4.1 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 3.42, 25.79, 26.28, 27.99, 28.45, 44.14, 67.22, 79.29, 81.38. Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.78; H, 10.55.

1-[(*S*)-2-*N*-(benzyloxycarbonyl)pyrrolidinyl]-2-butyn-1-one (5a): chromatography solvent AcOEt/hexane, 20:80, R_f 0.20, yield 86%, yellowish oil; IR (cm^{-1}, $CHCl_3$) 2991, 2221, 1699, 1633, 1452, 1416, 1354; MS (EI, 70 eV) 272 (M + H^+, 100), 228 (8), 204 (32); ^1H NMR ($CDCl_3$, 330 K) δ 1.94 (CH_3), 1.81−2.26 (m, 4 H), 3.58 (t, 2 H, ^3J = 6.7 Hz), 4.39 (m, 1 H), 5.13 (bs, 2H), 7.25−7.48 (m, 5 H); ^{13}C NMR ($CDCl_3$) two rotamers δ 4.04, 23.23, 23.89, 28.86, 30.06, 46.46, 47.00, 66.23, 66.66, 66.82, 66.89, 77.63, 78.10, 92.95, 93.35, 127.76, 128.20, 128.27, 136.21, 136.58, 154.21, 154.73, 186.70, 187.29. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.70; H, 6.05; N, 5.06. $[\alpha]^{20}_D$ = −36.6 (c = 5.09, CH_2Cl_2).

1-Phenyl-2-methoxyhex-4-yn-3-one (5b): chromatography solvent Et_2O/hexane, 10:90, R_f 0.20, yield 89%; IR (cm^{-1}, $CHCl_3$) 2220, 1671; MS (EI, 70 eV) 170 (17), 155 (3), 135 (100), 105 (15), 103 (46), 91 (25); ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.03 (ABX system, δ_A = 3.09, δ_b = 2.95, J_{AX} = 8.5 Hz, J_{BX} = 4.5 Hz, J_{AB} = 15 Hz), 3.35 (s, 3H), 3.90 (X part of an ABX system, J_{AX} = 8.5, Hz, J_{BX} = 4.5 Hz), 7.23−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 4.38, 38.29, 58.48, 78.39, 88.20, 94.90, 126.65, 128.34, 129.30, 136.72, 188.80. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.17; H, 6.91. $[\alpha]^{20}_D$ = −19.4 (c = 5.05, CH_2Cl_2).

Addition to Ketones: Method b. Propynyllithium was prepared using the procedure described above. The cold propynyllithium solution (15.5 mmol) was quickly added to a stirred suspension of dry $CeCl_3$ (15.5 mmol) in dry THF (10 mL) at −78 °C and the mixture stirred at this temperature for an additional 1 h. The ketone (10 mmol) in THF (50 mL) was slowly added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C before being allowed to warm to room temperature. A saturated solution of NH_4Cl (10 mL) was added, and the product was extracted with Et_2O (3 × 30 mL). The organic layer was washed with brine (2 × 50 mL) and dried over Na_2SO_4. After filtration the ether layer was concentrated *in vacuo*. Flash chromatography using the Still procedure (SiO_2, Et_2O−hexane) afforded the pure propargylic alcohol in high yield.

1-Methyl-1-phenyl-2-butyn-1-ol (4a): chromatography solvent Et_2O/hexane, 30:70, R_f 0.30, yield 92%, white solid, mp 42 °C; IR (cm^{-1}, $CHCl_3$) 3616, 3446, 2250, 1631; MS (CI, 70 eV) 160 (1), 159 (13), 145 (100); ^1H NMR ($CDCl_3$) δ 1.76 (s, 3H), 1.93 (s, 3H), 2.46 (s, 1H), 7.29−7.42 (m, 2H), 7.67 (d, 2H, ^3J = 7.7 Hz); ^{13}C NMR ($CDCl_3$) δ 3.58, 33.30, 69.91, 81.00, 82.88, 124.88, 127.43, 128.12, 146.02. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.56; H, 7.62.

1-(1-Propynyl)-2-isobutoxycyclopent-2-en-1-ol (4b): chromatography solvent Et_2O/hexane, 10:90, R_f 0.43, yield 89%, yellow oil; IR (cm^{-1}, $CHCl_3$) 3598, 3446, 2939, 2239. MS (CI, 70 eV) 194 (15), 138 (24), 120 (78), 91 (100); ^1H NMR ($CDCl_3$) mixture of diastereomers I and II δ 0.92 (t, 3H, ^3J = 7.4 Hz, dia I or II), 0.95 (t, 3H, ^3J = 7.4 Hz, dia I or II), 1.25 (d, 6H, ^3J = 6.1 Hz, dia I and II), 1.55−1.76 (m, 4H, dia I and II), 1.89 (d, 3H, dia I and II), 3.93 (q, 1H, ^3J = 6.1 Hz, dia I or II), 3.99 (q, 1H, ^3J = 6.1 Hz, dia I or II), 4.54 (t, 2H, ^3J = 2.25 Hz, dia I and II); ^{13}C NMR ($CDCl_3$) mixture of diastereomers δ 3.61, 3.71, 9.55, 9.74, 18.55, 18.77, 24.88, 28.59, 28.74, 39.03, 39.14, 75.53, 76.79, 80.05, 80.74, 96.11, 96.25, 157.52. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.09; H, 9.54.

1-(1-Propynyl)cyclopentanol (4c): chromatography solvent Et_2O/hexane, 20:80, R_f 0.26, yield 90%, colorless oil; IR (cm^{-1}, $CHCl_3$) 3600, 3447, 2974, 2242. MS (EI, 70 eV) 124 (1.5), 123 (1.2), 109 (27), 67 (100); ^1H NMR ($CDCl_3$) δ 1.62–1.79 (m, 11H), 2.58 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 3.26, 22.99, 42.02, 74.18, 78.50, 83.11. Anal. Calcd for $C_8H_{12}O$: no satisfactory elemental analysis was obtained due to the volatility of the product.

1-(1-Propynyl)indan-1-ol (4d): chromatography solvent Et_2O/hexane, 30:70, R_f 0.30, yield 95%, yellow oil; IR (cm^{-1}, $CHCl_3$) 3591, 3434, 2976, 2244, 1631; MS (CI, 70 eV) 172 (100), 157 (35), 155 (58), 144 (41), 129 (63), 127 (67); ^1H NMR ($CDCl_3$) δ 1.90 (s, 1H), 2.28 (s,1 H), 2.35–2.66 (m, 2 H), 2.76–3.25 (m, 2H), 7.22–7.38 (m, 3H), 7.49–7.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 3.01, 28.77, 42.53, 75.64, 80.34, 80.89, 122.46, 124.19, 126.21, 127.98, 142.15, 145.40. Anal. Calcd for $C_{12}H_{12}O$: C, 83.68; H, 7.02. Found: C, 82.88; H, 6.94.

1-(1-Propynyl)-2-cyclohexen-1-ol (4e): chromatography solvent Et_2O/hexane, 20:80, R_f 0.32, yield 88%, colorless oil; IR (cm^{-1}, $CHCl_3$) 3587, 3442, 2976, 2937,2218, 1703, 1650; MS (EI, 70 eV) 136 (2), 135 (6), 108 (100); ^1H NMR ($CDCl_3$) δ 1.68–2.17 (m, 7H), 1.84 (s, 3H), 5.72 (d, 1H, ^3J = 9.9 Hz), 5.80 (dt, 1H, ^3J = 3.1 Hz, ^3J = 9.9 Hz); ^{13}C NMR ($CDCl_3$) δ 3.45, 19.00, 24.44, 37.42, 76.37, 79.53, 82.95, 128.82, 130.84. Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 78.64; H, 8.86.

3β-(Tetrahydropyranyloxy)-chol-5-en-22-yn-20(*R*,*S*)-ol (4f): chromatography solvent ethyl acetate/hexane, 10:90, R_f 0.23, yield 86%, white solid, mp 164–165 °C; IR (cm^{-1}, $CHCl_3$) 3620, 3443, 2914, 2246; MS (CI, 70 eV) 441 (4) 440 (4), 423 (6), 356 (18), 339 (24), 321 (43); ^1H NMR ($CDCl_3$) only representative chemical shifts are reported for this compound δ 0.94 (s, 3H), 1.01 (s, 3H), 1.44 (s, 3H), 1.81 (s, 3H), 2.08–2.37 (m, 4H), 3.45–3.55 (m, 2H), 3.90 (m, 1H), 4.71 (bs, 1H), 5.35 (bs, 1H); ^{13}C NMR ($CDCl_3$) mixture of two diastereomers δ 3.56, 13.27, 19.32, 19.95, 20.73, 24.14, 25.10, 25.40, 29.59, 31.18, 31.28, 31.80, 32.69, 36.74, 37.12, 37.35, 38.66, 40.14, 43.04, 50.01, 56.23, 60.35, 62.73, 71.23, 75.84, 81.11, 82.99, 96.70, 96.81, 121.29, 121.36, 140.91, 141.09. Anal. Calcd for $C_{29}H_{44}O_3$: C, 79.04; H, 10.06. Found: C, 79.20; H, 10.07.

Addition to Acid Chlorides: Method c. The propynyllithium was prepared using the procedure described above. A solution of anhydrous $ZnCl_2$ (11 mmol, 1.5 g) in THF (5 mL) was dropwise added at −20 °C and stirred for 15 min before being allowed to warm to 0 °C for an additional 15 min. $Pd(PPh_3)_4$ (0.5 mmol, 0.577 g) was added in one portion to the reaction mixture at 0 °C, followed by the acid chloride (10 mmol) in THF (3 mL). The reaction mixture was stirred for 30 min and hydrolyzed with a saturated solution of NH_4Cl (10 mL). The product was extracted with Et_2O (3 × 30 mL). The organic layer was washed with a solution of saturated sodium chloride (2 × 50 mL) and dried over Na_2SO_4. After filtration the ether layer was concentrated *in vacuo*. Flash chromatography using the Still procedure (SiO_2, Et_2O–hexane) afforded the pure ketone in high yield.

1-Phenyl-2-butyn-1-one (5c): chromatography solvent Et_2O/hexane, 5:95, R_f 0.26, yield 90%, colorless oil; IR (cm^{-1}, $CHCl_3$) 3021, 2244, 1641, 1590; MS (EI, 70 eV) 144 (100), 115 (70), 77 (11), 67 (49); ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 7.46 (2 superimposed t, 2H, ^3J = 7.5 Hz), 7.59 (t, 1H, ^3J = 7.5 Hz), 8.14 (d, 2H, ^3J = 7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 4.08, 78.91, 92.36, 128.23, 129.26, 133.74, 136.79, 178.14. Anal. Calcd for $C_{10}H_8O$: C, 83.31; H, 5.59. Found: C, 83.50; H, 5.71.

1-Phenyl-1-hexen-4-yn-3-one (5d): chromatography solvent Et_2O/hexane, 10:90, R_f 0.26, yield 78%, yellow oil; IR (cm^{-1}, $CHCl_3$) 3019, 2220, 1630, 1600, 1268; MS (EI, 70 eV) 170 (51), 169 (100), 141 (59), 115 (21); ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 7.29 (AB system, 2H, δ_A= 7.81, δ_B = 6.76, J_{AB} = 16 Hz), 7.39–7.45 (m, 3H), 7.55–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 4.21, 78.52, 90.75, 128.41, 128.51, 128.98, 130.97, 134.02, 148.25, 178.57. Anal. Calcd for $C_{12}H_{10}O$: C, 84.68; H, 5.92. Found: C, 84.44; H, 5.71.

Acknowledgment. We thank the CNRS for providing a grant to D. Toussaint, and F. D'Aniello for performing the experiment entry 11.

JO950138D