Sodium Diethyldialkynylaluminate, A New Chemoselective Alkynylating Agent

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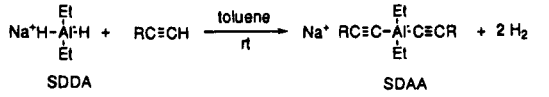
Alkynylation is an important reaction in organic synthesis, and it has been traditionally carried out by using alkali metal (Na, Li) alkynides or alkynyl Grignard reagents. Alkali metal alkynides react with aldehydes and ketones at low temperature to give good yields of the corresponding propargyl alcohols.[1] However, they also react with alkyl halides,[2] epoxides,[3] esters,[4] and amides[5] to give moderate yields of the corresponding products. Alkynyl Grignard reagents react similarly.[6–8] On the other hand, alkynylalanes have proved to be valuable reagents for coupling tertiary alkyl–alkynyl groups, for opening epoxides, and in conjugated addition to α,β-unsaturated carbonyl compounds.[9–11]

Recently we found that the reaction of sodium diethyldihydroaluminate (SDDA) with excess terminal acetylenes evolved only 2.0 equiv of hydrogen at room temperature in 3 h and ethyl groups of SDDA remained intact in the presence of terminal acetylenes. Therefore, sodium diethyldialkynylaluminate (SDAA) was easily prepared by adding 2.0 equiv of a terminal acetylene to SDDA at room temperature (Scheme 1).

Reactions of SDAA with representative carbonyl compounds (Scheme 2) and the chemoselectivity have been examined, and the results are summarized in Tables 1 and 2. As shown in Table 1, all the aldehydes and ketones examined were readily alkynylated to the corresponding propargyl alcohols in good yields under mild conditions. Using phenylacetylene, aliphatic and aromatic carbonyl compounds were readily alkynylated to the corresponding propargyl alcohols in 83–95% yields. Addition using the reagent derived from heptyne (more basic acetylide) proceeded in high yield with benzaldehyde, but the reactions with hexanal, 2-heptanone, and cyclohexanone were less efficient (67–75% yield), presumably due to competitive deprotonation. Other alkali metal alkynides are reported to react with carbonyl compounds to provide the corresponding products in 60–80% yields. In most cases the reactions must be carried out at low (−30 to −78 °C) temperatures.[1]

SDAA was found to be an excellent 1,2-alkynylating agent of cyclic or acyclic α,β-unsaturated carbonyl compounds. Thus SDAA regioselectively alkynylated 2-cyclohexen-1-one, cinnamaldehyde, and benzalacetone to provide the corresponding 1,2-addition products exclusively. The use of sodium acetylide and ethynylmagnesium bromide has been reported to give mainly 1,2-addition products from conjugated enones; however, the yields were moderate.[12,13] In contrast, alkynylalanes were found to react with enones, which are capable of

Scheme 1



Scheme 2

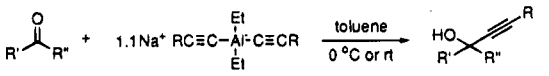
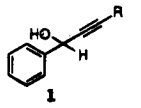
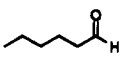
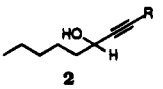
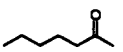
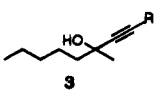
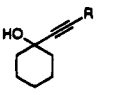
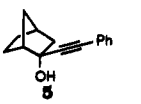
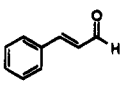
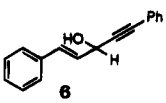
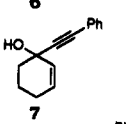
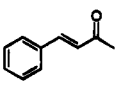
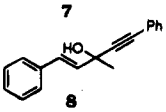


Table 1. Reaction of SDAA with Carbonyl Compounds in Toluene[a]

Compound	Product	Temp	Time		Yield(%)[b]
	 1	0°C	1h	1a R=Ph	95
		0°C	1h	1b R=C_5H_{11}	89
	 2	0°C	1h	2a R=Ph	90
		0°C	1h	2b R=C_5H_{11}	75
	 3	0°C	1h	3a R=Ph	84
		0°C	1h	3b R=C_5H_{11}	64
	 4	0°C	1h	4a R=Ph	87
		0°C	1h	4b R=C_5H_{11}	66
	 5	rt	1h		85
	 6	rt	1h		92
	 7	rt	1h		83
	 8	rt	3h		83

[a] Reactions were carried out by adding 5 mmol of carbonyl compound to 5.5 mmol of SDAA. [b] Isolated yields.

(1) (a) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1988; p 79. (b) Fisch, A.; Coisne, J. M.; Figeys, H. P. *Synthesis* **1982**, 211. (c) Cameron, M. D. U.S. Pat. 3,153,097 (1962–1964), Monsanto Co.; *Chem. Abstr.* **1965**, *62*, 1579. (d) Corriu, R. J. P.; Huynh, V.; Moreaw, J. J. E. *Tetrahedron Lett.* **1974**, *25*, 1887. (e) Saunders, J. H. In *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 416.

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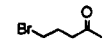
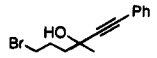
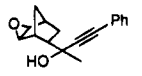
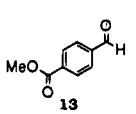
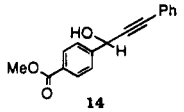
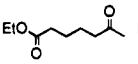
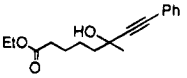
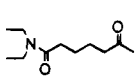
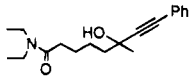
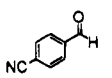
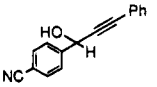
Table 2. Chemoselective Alkynylation of Carbonyl Compounds with $Et_2Al(PhC{\equiv}C)_2Na$ at 0 °C in Toluene,[a] in Comparison with PhC≡CLi and PhC≡CMgBr

Compound	Product	Reagent	Time	Yield(%)[b]
 9	 10	$Et_2Al(PhC{\equiv}C)_2Na$	12h	79[c]
		PhC≡CLi	1h	10[c](15)[d,e]
		PhC≡CMgBr	1h	70
 11	 12	$Et_2Al(PhC{\equiv}C)_2Na$	6h	95
		PhC≡CLi	1h	50(59)[d]
		PhC≡CMgBr	1h	28
 13	 14	$Et_2Al(PhC{\equiv}C)_2Na$	1h	88
		PhC≡CLi	1h	50(85)[d]
		PhC≡CMgBr	1h	72
 15	 16	$Et_2Al(PhC{\equiv}C)_2Na$	4h	82
		PhC≡CLi	1h	60(82)[d]
		PhC≡CMgBr	1h	68
 17	 18	$Et_2Al(PhC{\equiv}C)_2Na$	6h	83
		PhC≡CLi	1h	80(92)[d]
		PhC≡CMgBr	1h	41
 19	 20	$Et_2Al(PhC{\equiv}C)_2Na$	1h	92
		PhC≡CLi	1h	30(44)[d]
		PhC≡CMgBr	1h	35

[a] Reactions were carried out by adding 5 mmol of carbonyl compound to 5.5 mmol of SDAA. [b] Isolated yields. [c] At −20 °C. [d] At −50 °C. [e] 2-Methyl-2-(phenylethynyl)tetrahydrofuran was the major product (90% at 0 °C and 85% at −50 °C).

adopting a cisoid conformation (such as benzalacetone) to provide products arising exclusively from 1,4-addition.[11]

SDAA was found to be highly chemoselective. Thus the reagent did not affect other functional groups such as epoxides (1,2-epoxybutane), esters (ethyl benzoate and ethyl caproate), amides (*N,N*-dimethylbenzamide and hexanoyl piperidine), and nitriles (benzonitrile and hexanenitrile) at 0 °C. Halogen compounds such as methyl iodide, benzyl chloride, and *tert*-butyl bromide were also inert to SDAA even at room temperature. We have evaluated the selectivity of SDAA and also for comparison the corresponding lithium phenylacetylide and (phenylethynyl)magnesium bromide, using several functionalized carbonyl compounds. The results are summarized in Table 2. As shown in Table 2, SDAA reacted quite selectively with aldehydes or ketones in the presence of bromide, epoxide, ester, amide, and nitrile functionalities. For example, SDAA reacted with 5-bromo-2-pentanone (**9**) to give 5-bromo-2-(phenylethynyl)pentan-2-ol (**10**) in an isolated yield of 79% at −20 °C. In contrast, lithium phenylacetylide gave 2-methyl-2-(phenylethynyl)tetrahydrofuran in 90% yield at 0 °C (85% even at −50 °C) instead of the expected product **10**. The observed formation of a tetrahydrofuran derivative presumably demonstrates the greater nucleophilicity of the lithium alkoxide than that of the aluminum alkoxide resulting from use of SDAA reagent. The high chemoselectivity of SDAA was also shown by the reaction with 5-acetyl-2,3-epoxybicyclo[2.2.1]heptane (**11**) to give selectively the product with an unaffected epoxide 1-(2,3-epoxybicyclo-[2.2.1]heptan-5-yl)-1-(phenylethynyl)ethan-1-ol (**12**) in excellent yield (95%) at 0 °C. In the reactions with 4-carbomethoxybenzaldehyde (**13**) and ethyl 6-oxoheptanoate (**15**), SDAA selectively alkynylated carbonyl groups in the presence of esters to give the corresponding propargyl alcohols in yields of 88% and 82%, respectively. Both lithium phenylacetylide and (phenylethynyl)magnesium bromide gave lower yields of desired product at 0 °C, but improved yields were observed when the reaction with the former was carried out at −50 °C. However, in the reaction with *N,N*-diethyl-6-oxoheptanamide (**17**), in contrast to the (phenylethynyl)magnesium bromide reaction, both SDAA and lithium phenylacetylide gave the alkynylated product **18** in good yields at 0 °C. Finally, SDAA reacted with 4-cyanobenzaldehyde (**19**) to give the desired product in an excellent yield (92%) at 0 °C. Both lithium phenylacetylide and (phenylethynyl)magnesium bromide were less effective. It may be too early at this point to attempt to answer why SDAA has such a unique selectivity. However, the following are believed to be mainly responsible for the unique selectivity of SDAA: the lower reactivity of the aluminum–alkynyl bond when compared with those of lithium and magnesium; the Lewis base structure of SDAA in contrast to the Lewis acid structure of alkynylalane; the high affinity of aluminum to the oxygen atom.

In conclusion, sodium diethyldialkynylaluminate (SDAA) is a good alternative alkynylating agent which exhibits good chemoselectivity in the presence of other functional groups such as halide, epoxide, ester, amide, and nitrile and an excellent regioselectivity in the reaction with α,β-unsaturated carbonyl compounds.

Experimental Section

Preparation of SDAA. Into a 150 mL flask under nitrogen, 19.4 mL (30 mmol) of a 1.54 M SDDA solution in toluene and 33.9 mL of toluene were introduced. The solution was maintained at room temperature, and then 6.7 mL (61.5 mmol) of phenylacetylene was added by vigorous stirring. The stirring was continued for an additional 3 h to complete hydrogen evolution. The SDAA solution thus prepared was 0.5 M in alkynide, as estimated by the reaction with excess benzaldehyde.

General Procedure for the Preparation of Propargyl Alcohols. The alkynylation of benzaldehyde is representative. Into a 50 mL flask was introduced 10 mL of toluene, followed by 11 mL (5.5 mmol) of 0.5 M SDAA. The solution was maintained at 0 °C, and 10 mL (5 mmol) of a 0.5 M solution of benzaldehyde in toluene was added. After 1 h the reaction mixture was hydrolyzed with 50 mL of saturated NH_4Cl, and the product was extracted with 50 mL of ethyl acetate. The ethyl acetate layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was chromatographyed on a silica gel column (eluent hexane/EtOAc/Et_3N 9:1:0.05) to give 0.99 g (95%) of 1-(phenylethynyl)-1-phenylmethanol (**1a**): ^1H NMR ($CDCl_3$) δ 2.50 (brs, 1H), 5.71 (s, 1H), 7.33–7.66 (m, 10H); IR (neat) 3356, 3063, 3032, 2876, 2229, 1599, 1491, 1444, 1278, 1031; GCMS *m/z* (relative intensity) (EI, 70 eV) 208 (M^+, 76), 77 (84), 102 (75), 103 (43), 105 (51), 129 (58), 130 (51). Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.30; H, 5.70.

1-(Phenylethynyl)-3-phenyl-2-propen-1-ol (6). Flash chromatography gave 1.08 g of **6** (92% yield): ^1H NMR ($CDCl_3$) δ 2.18 (brs, 1H), 5.30 (d, 1H, J = 5.9 Hz), 6.40 (dd, 1H, J = 5.9, 15.9 Hz), 6.86 (d, 1H, J = 15.9 Hz), 7.21–7.51 (m, 10H); IR (neat) 3317, 3059, 2321, 1620, 1599, 1491, 1253; GCMS *m/z* (relative intensity) (EI, 70 eV) 234 (M^+, 30), 77 (60), 105 (100), 129 (46), 233 (36). Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.12; H, 6.05.

1-(2,3-Epoxybicyclo[2.2.1]heptan-5-yl)-1-(phenylethynyl)-ethan-1-ol (12). Flash chromatography (hexane/EtOAc/Et_3N

(13) Shackelford, J. M.; Michalowicz, W. A.; Schwartzman, L. H. *J. Org. Chem.* **1962**, *27*, 1631.

5:5:0.05) gave 1.20 g of **12** (95% yield): ^{1}H NMR ($CDCl_3$) δ 1.2–1.3 (m, 1H), 1.41–1.67 (m, 5H), 1.68–1.8 (m, 2H), 2.3 (s, 1H), 2.46–2.56 (s, 1H), 2.62–2.75 (s, 1H), 3.09–3.23 (m, 2H), 7.28–7.48 (m, 5H); IR (neat) 3376, 3026, 2980, 2867, 2360, 1380, 1156, 1008; GCMS m/z (relative intensity) (EI, 70 eV) 254 (M^+, 1), 81 (21), 102 (13), 116 (16), 129 (18), 145 (100), 146 (16). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.22; H, 7.15.

***N,N*-Diethyl-6-hydroxy-6-(phenylethynyl)heptanamide (18).** Flash chromatography (eluent hexane/EtOAc/Et_3N 5:5:0.05) gave 1.25 g of **18** (83% yield): ^{1}H NMR ($CDCl_3$) δ 1.05–1.19 (m, 6H), 1.57 (s, 3H), 1.60–1.82 (m, 6H), 2.34 (t, 2H, J = 7.6 Hz), 2.51 (s, 1H), 3.22–3.43 (m, 4H), 7.26–7.42 (m, 5H); IR (neat) 3379, 2976, 2935, 1624, 1444, 1381, 1267, 1099; GCMS m/z (relative intensity) (EI, 70 eV) 55 (15), 58 (84), 72 (70), 86 (26), 100 (100), 102 (60), 115 (95), 128 (21). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.65; H, 9.07; N, 4.78.

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Supporting Information Available: Spectroscopic data for compounds **1b–5, 7–11, 13–17**, and **20** as well as the synthesis of **9,11,13,15**, and **17** (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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