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Sodium Trimethylethynylaluminate, a New Chemoselective Ethynylating Agent

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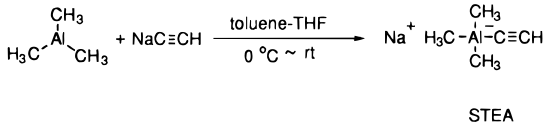
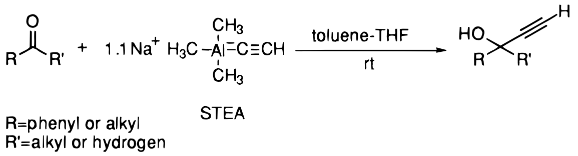
Ethynylation is an important reaction for extending carbon chains and introducing other functional groups in organic synthesis. Ethynylation has been traditionally carried out by using alkali metal (Na, Li) acetylides or ethynyl Grignard reagents,[1] but these reagents are sometimes difficult to prepare and react efficiently with carbonyl compounds. Thus, monolithium acetylide disproportionates into dilithium acetylide and acetylene in tetrahydrofuran at above −78 °C,[2] requiring preparation at −78 °C or a complexing agent like ethylenediamine that stabilizes monolithium acetylide. Alkali metal acetylides react with aldehydes and ketones at low temperature (−78 °C) to give good yields of the corresponding ethynyl carbinols,[3] but also give moderate yields in their reactions with alkyl halides,[4] epoxides,[5] esters,[6] and amides.[7] Ethynyl Grignard reagents react similarly.[8−10]

Recently, we reported the highly chemoselective reactions of sodium diethyldialkynylaluminate (SDAA)[11] with carbonyl compounds. SDAA reacts readily with carbonyl compounds, but does not react with many other functional groups such as halides, epoxides, esters, amides, and nitriles. SDAA also showed excellent 1,2-regioselectivity in the reactions with cyclic or acyclic α,β-unsaturated carbonyl compounds. However, one disadvantage of this reagent was that only one alkynyl group of SDAA was transferred in the alkynylation of carbonyl compounds. We report here a new chemoselective ethynylating agent, sodium trimethylethynylaluminate (STEA), which not only gives good yields of ethynyl carbinols at room temperature, but also exhibits excellent chemoselectivity and regiospecificity like SDAA.[11] STEA can be readily prepared by adding commercially available sodium acetylide to trimethylaluminum at 0 °C in toluene−THF (eq 1). THF is required as a cosolvent to get a clear solution since STEA is sparingly soluble in toluene alone. The addition of carbonyl compounds to this solution at room temperature produced the corresponding ethynyl carbinols in good yield (eq 2).



(1)



(2)

Reactions of STEA with representative carbonyl compounds have been examined, and the results are summarized in Table 1. As shown in the Table 1, all the aldehydes and ketones examined were readily ethynylated with STEA to afford the corresponding ethynyl carbinols in 73−93% yields under mild conditions. The ethynylation of benzaldehyde gave 1-phenyl-2-propyn-1-ol (**1**) in an isolated yield of 93% at room temperature. However, sodium acetylide in liquid ammonia[3a] and lithium acetylide in tetrahydrofuran[3b] are known to produce **1** at −78 °C in 82−84% and 93% yields, respectively. The ethynylation of aliphatic carbonyl compounds such as hexanal, 2-heptanone, cyclohexanone, and norcamphor provided the expected ynols in slightly lower yields (80−88%) as compared with benzaldehyde, possibly due to deprotonation. Hexanal was ethynylated to give a 80% yield of 1-octyn-3-ol (**2**). Using lithium acetylide in tetrahydrofuran, the ethynylation of hexanal has been reported to give 1-octyn-3-ol in 98% yield at −78 °C, but a decreased yield of 39% at 0 °C due to the irreversible formation of a dilithium acetylide.[3b] In the case of cyclohexanone, we could conveniently obtain 1-ethynylcyclohexanol (**4**) in 81% yield at room temperature, but the ethynylation with sodium acetylide in liquid ammonia[12] is known to produce only 65−75% yield of **4**.

STEA was found to be an excellent 1,2-ethynylating agent of cyclic or acyclic α,β-unsaturated carbonyl compounds. Thus, STEA regioselectively ethynylated 2-cyclohexen-1-one, cinnamaldehyde, and benzalacetone to provide the corresponding 1,2-addition products exclusively. It has been reported that sodium acetylide and ethynylmagnesium bromide also gave mainly 1,2-addition products from conjugated enones.[13,14] However, the 1,2-ethynylation with sodium acetylide had to be carried out at −80 °C to get a good yield (72−79%),[13] and the reaction of ethynylmagnesium bromide with cinnamaldehyde gave 1-phenyl-1-penten-4-yn-3-ol (**6**) in yields ranging from 58% to 69%.[14] But STEA produced **6** in higher yield (84%) at room temperature.

STEA was also found to be highly chemoselective. Thus, the reagent did not react with representative halides (benzyl chloride and octyl bromide), an epoxide

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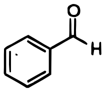
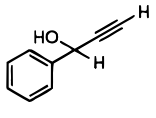
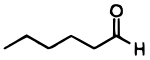
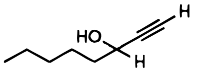
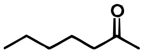
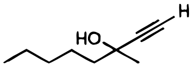
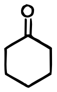
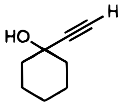
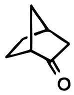
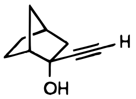
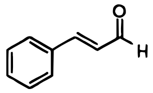
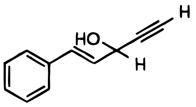
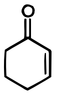
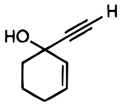
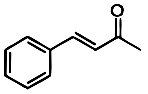
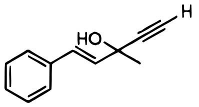
Table 1. Reaction of STEA with Carbonyl Compounds in Toluene–THF[a]

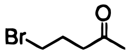
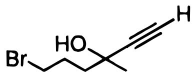
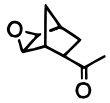
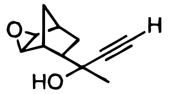
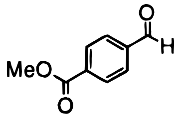
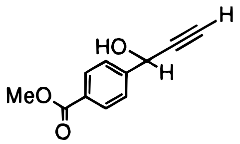
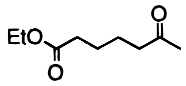
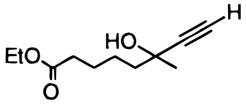
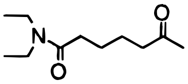
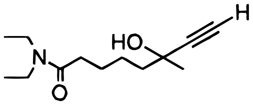
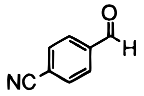
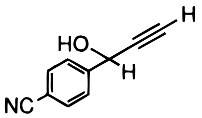
Compound	Product	Time	Yield(%)[b]
	 **1**	1h	93
	 **2**	1h	80
	 **3**	3h	88
	 **4**	3h	81
	 **5**	1h	82
	 **6**	1h	84
	 **7**	1h	73
	 **8**	3h	78

[a] Reactions were carried out by adding 5 mmol of carbonyl compound to 5.5 mmol of STEA at room temperature.

[b] Isolated yields.

(cyclohexene oxide), an amide (*N*,*N*-dimethyldodecanamide), and nitriles (benzonitrile and hexanenitrile) at room temperature, and esters (ethyl benzoate and ethyl caproate) at 0 °C. We have studied the chemoselectivity of STEA in reactions with functionalized ketones and aldehydes, and the results are summarized in Table 2. As shown in the Table 2, STEA reacted quite selectively with aldehydes or ketones in the presence of bromide, epoxide, ester, amide, and nitrile functionalities. For example, STEA reacted with 5-bromo-2-pentanone (**9**) at −5 °C to give 6-bromo-3-methyl-1-hexyn-3-ol (**10**) in an isolated yield of 87%. In contrast, lithium phenylacetylide is known to give 2-methyl-2-(phenylethynyl)tetrahydrofuran in 90% yield (85% even at −50 °C) instead of the desired 5-bromo-2-(phenylethynyl)pentan-2-ol.[11] However, the reaction with STEA did not produce the tetrahydrofuran derivative. In the reaction with the epoxy ketone **11,** STEA reacted selectively with the ketone in good yield (83%) leaving the epoxide unaffected. The high chemoselectivity of STEA was also shown by the selective ethynylation of ketone and aldehyde groups in oxo esters **13** and **15** to give the corresponding ethynyl carbinols (88% and 87%, respectively). In the reaction with *N*,*N*-diethyl-6-oxoheptanamide (**17**), STEA gave the ethynylated product **18** in a high yield of 91% at 0 °C and a similar yield of 88% even at room temperature. Finally, STEA reacted with 4-cyanobenzaldehyde (**19**) to give the ynol **20** in excellent yield (90%). It may be too early at this point to answer why STEA has such a unique selectivity. However, the lower reactivity of aluminum–ethynyl bond compared with those of alkali metal and magnesium, the Lewis base structure of STEA,

Table 2. Chemoselective Ethynylation of Carbonyl Compounds with STEA in Toluene–THF[a]

Compound	Product	Time(h)	Temp	Yield(%)[b]
 **9**	 **10**	6h	-5 °C	87
 **11**	 **12**	3h	0 °C	83
 **13**	 **14**	1h	0 °C	88
 **15**	 **16**	3h	0 °C	87
 **17**	 **18**	3h	0 °C	91
 **19**	 **20**	3h	0 °C	90

[a] Reactions were carried out by adding 5 mmol of carbonyl compound to 5.5 mmol of STEA.

[b] Isolated yields.

and the high affinity of aluminum to the oxygen atom are believed to be mainly responsible for the unique selectivity of STEA.

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

Experimental Section

General Procedure for the Preparation of Ethynyl Carbinols. The ethynylation of benzaldehyde is representative. A 100 mL flask under nitrogen was charged with 2.5 mL (5.0 mmol) of 2.0 M trimethylaluminum solution in toluene, 5.4 mL of toluene, and 3.0 mL of THF. The solution was cooled (0 °C), and 1.40 g (1.54 mL) of 18 wt % sodium acetylide (95% purity, 5.00 mmol) slurry in xylene was added dropwise with vigorous stirring. To the STEA solution (0.40 M in aluminate) at room temperature was added a toluene solution (10 mL) of benzaldehyde (5.0 mmol). After 1 h, 50 mL of saturated NH_4Cl was added, and the mixture was extracted with ethyl acetate. The organic extract was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude residue was chromatographed on a silica gel column (eluent hexane/EtOAc 9:1) to give 0.61 g (93%) of 1-phenyl-2-propyn-1-ol (**1**): ^1H NMR ($CDCl_3$) δ 2.51 (br s, 1H), 2.59 (d, 1H, $J = 2.2$ Hz), 5.47 (d, 1H, $J = 2.2$ Hz), 7.35–7.57 (m, 5H); IR (neat) 3373, 3288, 3065, 2878, 2117; GCMS *m/z* (relative intensity) (EI, 70 eV) 132 (M^+, 74), 51 (34), 53 (50), 77 (74), 78 (51), 89 (11), 103 (51), 114 (21), 131 (100). Anal. Calcd for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.67; H, 6.09.

1-Phenyl-1-penten-4-yn-3-ol (6). Flash chromatography gave 0.66 g of **6** (84% yield): ^1H NMR ($CDCl_3$) δ 2.06 (br s, 1H), 2.60 (d, 1H, $J = 2.4$ Hz), 5.04–5.08 (m, 1H), 6.31 (dd, 1H, $J = 15.9$, 5.9 Hz), 6.82 (d, 1H, $J = 15.9$ Hz); IR (neat) 3458, 3286, 2984, 2131, 1655; GCMS *m/z* (relative intensity) (EI, 70 eV) 158 (M^+, 37), 51 (72), 77 (52), 91 (70), 105 (100), 115 (72), 129 (69), 140 (17), 157 (43). Anal. Calcd for $C_{11}H_{10}O$: C, 83.51; H, 6.37. Found: C, 83.34; H, 6.34.

1-(2,3-Epoxybicyclo[2.2.1]heptan-5-yl)-1-ethynylethan-1-ol (12). Flash chromatography (eluent hexane/EtOAc 8:2) gave 0.74 g of **12** (83% yield): ^1H NMR ($CDCl_3$) δ 1.17–1.32 (m, 2H), 1.42–1.63 (m, 5H), 2.36 (s, 1H), 2.46–2.49 (m, 2H), 2.61–2.65 (m, 2H), 3.08–3.12 (m, 2H); IR (neat) 3371, 3225, 2980, 2937, 2102; GCMS *m/z* (relative intensity) (EI, 70 eV) 69 (90), 79 (94), 81 (100), 91 (34), 117 (15), 135 (4), 163 (9). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.02; H, 7.98.

***N*,*N*-Diethyl 6-hydroxy-6-methyl-7-ynheptanamide (18).** Flash chromatography (eluent hexane/EtOAc 4:6) gave 0.99 g of **18** (88% yield): ^{1}H NMR ($CDCl_3$) δ 0.91−1.30 (m, 6H), 1.49 (s, 3H), 1.53−1.78 (m, 6H), 2.29−2.40 (m, 1H), 2.42 (s, 1H), 2.46 (br s, 1H), 3.25−3.42 (m, 4H); IR (neat) 3383, 3308, 2976, 2936, 2104, 1624; GCMS *m*/*z* (relative intensity) (EI, 70 eV) 58 (100), 72 (93), 100 (44), 115 (52), 128 (20), 156 (56). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.26; H, 10.47; N, 6.06.

Acknowledgment. This work was supported by the Organic Chemistry Research Center/KOSEF.

Supporting Information Available: Spectroscopic data for compounds **2**−**5**, **7**−**11**, **13**−**17**, and **20**, as well as the synthesis of **9**, **11**, **13**, **15**, and **17** (4 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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