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Practical synthesis of functionalized terminal alkynes, 3,3,3-triethoxypropyne and ketal protected prop-2-ynones

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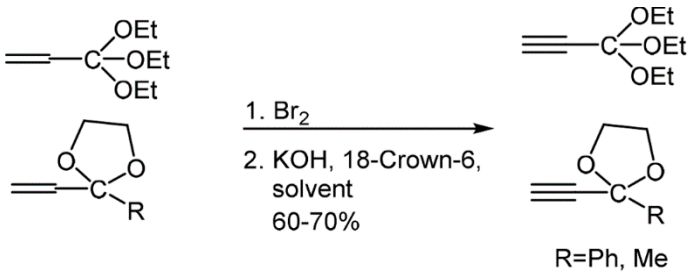
ABSTRACT

Practical and economical synthesis of synthetically valuable 3,3,3-triethoxypropyne, ketal protected phenyl and methyl substituent prop-2-ynones is described. Bromination and subsequent 18-Crown-6 catalyzed elimination of triethylorthoacrylate and ketal protected terminal alkenes with methyl and phenyl substituent which are inturn readily available from triethylorthopropionate, 3-chlorobutan-2-one and propiophenone afforded multigram quantities (>10 grams) of corresponding functionalized terminal alkynes. Exploration of the synthetic utility of these alkynes is also demonstrated by the acetylenic substitution of the phenylalaninol derived 1,2-cyclic sulfamidate to deliver chiral alkynylated amines.

GRAPHICAL ABSTRACT



KEYWORDS: 1,2-cyclic sulfamidates, ketal, orthoester, terminal alkynes

Introduction

During the course of our ongoing investigations focused on the reactivity profile of cyclic sulfamidates towards acetylides, economical and practical synthesis of functionalized terminal alkynes, 3,3,3-triethoxypropyne, ketal protected phenyl and methyl substituent prop-2-ynones on multigram quantities was required in order to scan the scope of the chemistry.[1] Cyclic sulfamidates[2] **1** readily undergo nucleophilic displacement with acetylides **2** to form *N*-sulfate intermediates **3** which could be hydrolyzed under acidic conditions to give alkynylated amines **4** in high yields (Scheme 1).

Introduction of the masked carbonyl functionality to the acetylide unit could enable synthesis of highly functionalized amines that provides a sound platform to develop further chemistry. Installation of the carbonyl group (or protected form) into alkynylated amine products called for the use of alkyl propiolates (or protected propiolates) and protected ynones as acetylide partners in the substitution reactions. Generation of the propiolate anion directly from methylpropiolate was found to be problematic. This failure may be attributable to the instability of the propiolate anion in solution through the inclination of the acetylenic moiety and alkyl

carboxylate group to react with each other.[3] Our attention subsequently moved to known triethylorthopropiolate as a synthetically more stable propiolate anion precursor.

A brief survey of literature on the synthesis of triethylorthopropiolate revealed that this compound can be prepared by a number of ways. Stetter's synthesis from triethyl orthopropionate using bromination and elimination reactions is not efficient due to low yielding dehydrobromination in the last step.[4a] Another synthesis by Boche involves use of expensive trimethylsilyl acetylene as starting material and reagents.[5a] Stetter's low yielding step was improved by Gassman using powdered KOH in the presence of 18-crown-6 ether as catalyst, but adequate experimental details were not reported in the letter.[6] Adaptation of this procedure for economical and practical multi gram synthesis of 3,3,3-triethoxypropyne in our hands led to several practically useful observations to be reported in this communication.[7] The synthesis and use of the ketal protected ynones with phenyl[8] and methyl[9,10] substituents have been reported in several papers. Most of the synthetic procedures rely on the direct protection of the expensive ynones with methyl and phenyl substituents. In these cases, side reactions hamper the efficiency of the protection with ethylene glycol resulting in only moderate yields.[8] As a result we needed a reliable, economical and practical synthesis of these valuable functionalized terminal alkynes on multigram scale. In this communication multigram synthesis of triethylorthopropiolate, ketal protected methyl and phenyl substituent alkynes from cheap starting materials triethylorthopropionate, 3-chlorobutan-2-one and propiophenone respectively is reported. Exploration of synthetic utility of these functionalized terminal alkynes is also demonstrated by the acetylenic substitution of phenylalaninol derived 1,2-cyclic sulfamidates to deliver chiral alkynylated amines.

Results Discussion

Synthesis of functionalized terminal alkynes

Triethylorthopropionate **5** was brominated with bromine in pyridine according to Stetter's procedure[4a] to yield mono brominated compound **6** which upon treatment with powdered KOH in DMSO eliminated to furnish triethylorthoacrylate **7** (Scheme 2). These first bromination and elimination reactions proceed efficiently on large scale without problem. The second bromination in DCM produced dibromo compound **8**. As the dibromide **8** was prone to decomposition on heat and chromatographic purification on silica (monitoring of the reaction was performed on alumina TLC), the compound was directly subject to the second elimination reaction. Slight less than stoichiometric amount of bromine (0.9 equivalent) was sufficient to carry out efficient bromination. Crude dibromide **8** was eliminated with powdered KOH in heptane in the presence of the crown ether catalyst to give multigram quantities of synthetically valuable 3,3,3-triethoxypropyne **9**. In addition to the use of bromine and powdered KOH, 4-(dimethylamino)pyridine tribromide as brominating agent and *t*-BuOK and LiHMDS as base were investigated to obtain high yield of **9** without any practical improvements. The use of bromine (0.9 equiv.) in DCM in the bromination step and powdered KOH in heptane in the presence of 18-crown-6 catalyst in the elimination step is the most practical and efficient combination to produce 3,3,3-triethoxypropyne **9** as clear oil of high purity in 61% yield over two steps. By this way we prepared 3,3,3-triethoxypropyne **9** several times in multigram quantities (30 g).

Propiophenone **10** was brominated according to the literature procedure[11] to obtain give α-bromo ketone **11** before protection by the treatment of ethylene glycol with PTSA catalyst. It is worth noting that since the α-bromo ketone **11** was a highly irritant for skin and eyes, caution should be taken strictly for multigram synthesis. Elimination reaction of **12** with powdered KOH in DMSO afforded alkene **13**. Similarly, application of the use of bromine (0.9 equiv.) in the

bromination step and powdered KOH in heptane in the presence of 18-crown-6 catalyst in the elimination step on the dibromide **14** allowed the synthesis of 2-ethynyl-2-phenyl-1,3-dioxolane **15** as clear oil of high purity in 70% yield over two steps.

3-Chlorobutan-2-one **16** was protected as ketal derivative on the treatment with ethylene glycol under acidic condition to obtain the known chloro ketal **17** (Scheme 4).[12] Elimination of **17** on exposure to powdered KOH furnished **18**. Bromination of the double bond was achieved with bromine to yield the dibromide compound **19**. Performing second elimination in heptane lead to difficulties in purification of 2-ethynyl-2-methyl-1,3-dioxolane **20** during distillation. Nonpolar solvent with higher boiling point was necessary in order to make separation by distillation efficiently. Thus, the second elimination was conducted in *n*-dodecane (b.p. 214–218°C) with powdered KOH in the presence of 18-crown-6 catalyst to deliver 2-ethynyl-2-methyl-1,3-dioxolane **20** as clear oil of high purity in 60% yield over two steps.

Synthetic utility of functionalized terminal alkynes

Exploration of the synthetic utility of the synthesized terminal alkynes was also demonstrated by the acetylenic substitution of phenylalaninol derived 1,2-cyclic sulfamidates **21** (Scheme 5). Functionalized terminal alkynes **9**, **15** and **20** was lithiated with the action of *n*-butyllithium in THF at –10°C. Nucleophilic cleavage of the 1,2- cyclic sulfamidate **21** with the resulting acetylides **22** and **25** produced *N*- sulfate **23** and **26** intermediates. Acidic hydrolysis of **23** was performed with the use of 5M HCl condition which is generally considered to be the standard condition to liberate the nitrogen atom. During hydrolysis the orthoester group was hydrolyzed concurrently to afford functionalized alkynylated amino ethylester **24** in high yield.[13] Two equivalent of the acetylide component **22** was required for the complete consumption of **21**.

Similarly, acetylenic displacement reactions of **21** with ketal protected acetylides **25** also produced the corresponding *N*- sulfate **26** intermediates. Due to the instability of the ketal group to 5M HCl conditions, acidic hydrolysis of **26** was performed with H_2SO_4 in these cases to be able to obtain ketal protected alkynylated amines **27** in good yields. Synthetic utility of the alkynylated amino ethyl ester **24** for asymmetric synthesis of piperidones was already reported.[13] Evaluation of the functionalized ketal protected alkynylated amines **27** for synthesis of *N*-heterocycles will be reported elsewhere.

Conclusion

In summary practical and economical synthesis of 3,3,3-triethoxypropyne **9**, ketal protected prop-2-ynones with phenyl **15** and methyl **20** substituents from cheap starting materials on multigram quantities is reported. Synthetic utility of these alkynes is also illustrated by the acetylenic substitution of phenylalaninol derived 1,2-cyclic sulfamidate **21** to deliver chiral alkynylated amines.

Experimental

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian AS 400 MHz NMR spectrometer with TMS as an internal. Chemical shifts are expressed in δ (parts per million) units downfield from TMS. Coupling constants (*J*) are quoted to the nearest 0.5 Hz. IR spectra were recorded on a Perkin Elmer Spectrum BX spectrometer as thin films on NaCl plates. Mass Spectra were taken from TUBITAK Marmara Research Centre (MAM), Gebze, Istanbul, and DAYTAM, Ataturk University, Erzurum, Turkey. Optical rotations were measured with Rudolph Research Analytical Autopol I Automatic Polarimeter. THF and ether were freshly distilled from $LiAlH_4$ before use. TLC was performed using aluminium plates coated with silica gel (254 nm) and use of

the basic permanganate dying system. Flash column chromatography was carried out using silica gel (0.063–0.2 mm). Removal of solvents in *vacuo* was achieved using an IKA rotary evaporator at room temperature unless otherwise stated. Yields refer to isolated material, homogeneous by TLC and NMR spectroscopy, unless otherwise stated.

Synthesis of 3,3,3-triethoxypropyne 9

2-Bromo-1,1,1-triethoxypropane 6[4a]

To a solution of triethylorthopropionate **5** 110 g (0.625 mol) in 50 mL pyridine cooled over ice-bath was added bromine (32 mL, 102 g, 0.64 mol) dropwise. The resulting reaction mixture was stirred over the bath for 3 hours. Pyridinium bromide salts began to form as the reaction progressed. The reaction mixture was diluted with hexane and filtered through Celite®. Evaporation of the solvents in *vacuo* gave the crude product. Purification by distillation afforded 2-bromo-1,1,1-triethoxypropane **6** (127.54 g, 80% yield) as a pale yellow oil; b.p 87°C/15 mmHg, (Lit.[4a], 74–75°C/10 mmHg). The compound was directly subjected to elimination step without characterization.

3,3,3-triethoxyprop-1-ene 7[4a]

A mixture of monobromoorthoester **6** (120.6 g, 0.40 mol) and KOH (111.6 g, 1.98 mol) in 350 mL DMSO was heated gradually to 120°C for 3 hours with stirring. The reaction mixture was cooled to room temperature and diluted with water to dissolve insoluble material. Extraction of the resulting solution was performed with Et_2O (3 × 250 mL). Combined organics was dried over Na_2CO_3, filtered and evaporated in *vacuo* to give crude the acrylate product. Purification by distillation furnished 3,3,3-triethoxyprop-1-ene **7** (54.4 g, 78% yield) as a clear oil; b.p 54–

55°C/15 mmHg, (Lit.[4a], 78–79°C/36 mmHg);^{1}H NMR δ_H (400 MHz, $CDCl_3$) (ppm): 1.15 (9H, t, *J*=7.2), 3.44 (6H, q, *J*=7.2), 5.37 (1H, dd, *J*=2.8 and 10), 5.54 (1H, dd, *J*=2.8 and 17.2), 5.62 (1H, dd, *J*=10 and 17.2).

3,3,3-triethoxypropyne 9[4a]

To a solution of the acrylate (50.1 g, 288 mmol) in 300 mL DCM cooled at –10°C with ice-salt bath was added a solution of bromine (41.1 g, 258 mmol) in 100 mL DCM dropwise over 1 hour. The resulting pale yellow solution was stirred at this temperature for additional 30 minutes. Evaporation of volatiles in *vacuo* produced the crude dibromide compound **8**. Since this compound was prone to decomposition, the crude product was directly subjected to elimination step without purification or characterization.

To a mixture of powdered KOH (40.5 g, 720 mmol) and 18-crown-6 (800 mg) in 300 mL heptane was carefully added a solution of the crude dibromide in 75 mL heptane at room temperature. The resulting reaction mixture began to warm up. It is essential at this point that the mixture be heated gradually in a controlled manner to the refluxing temperature in order to avoid uncontrolled heating up (rapid heating may lead to uncontrolled reactions and extensive decomposition which reduces the reaction yield significantly). The pale yellow mixture was heated to reflux for 6 hours. The reaction mixture was cooled to room temperature and diluted with 300 mL hexane and 300 mL water to dissolve insoluble material. The organic phase was separated, washed with brine, dried over Na_2CO_3, filtered and evaporated in *vacuo* to give crude triethylorthopropiolate. Purification by fractional distillation afforded 3,3,3-triethoxypropyne **9** (30.3 g, 61% over two steps) as a clear oil; b.p 67–68 °C/15 mmHg, (Lit.[4a], 83°C/32 mmHg); IR

(film) υ_{max}/cm^{-1} 3266, 2118, 658 (HC≡C-);^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 1.24 (9 H, t, *J*=7.2), 2.55 (1H, s), 3.7 (6H, q, *J*=7.2).

Synthesis of 2-ethynyl-2-phenyl-1,3-dioxolane 15

2-bromo-1-phenylpropan-1-one 11[11]

To a solution of propiophenone 10 (64 g, 0.48 mol) in 240 mL acetic acid cooled over ice bath was added bromine (82.2 g, 0.51 mol) dropwise. The resulting reaction mixture was stirred at this temperature for 1 h and then allowed to warm up to room temperature with stirring for additional hour. The reaction mixture was neutralized saturated $NaHCO_3$ solution. Extraction was carried out with DCM (2 × 250 mL). Combined organics was dried over Na_2SO_4 and evaporated in *vacuo* to give the crude bromoketone. Purification by distillation afforded 2-bromo-1-phenylpropan-1-one **11** (93.66 g, 94%) as a clear oil; b.p 112°C/15 mmHg, (Lit.[11],

135–144°C/19 mmHg); TLC R*f*:0.42 [hexane]; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H (ppm): 1.90 (3H, d, *J*=6.4), 5.29 (1H, q, *J*=6.4), 7.46-7.51 (2H, m, Ar-H), 7.56–7.61 (1H, m, Ar-H), 8.01-8.04 (2H, m, Ar-H). Note that the α-bromo ketone **11** was a highly irritant for skin and eyes, caution should be taken strictly.

2-(1-bromoethyl)-2-phenyl-1,3-dioxolane 12[11]

A mixture of bromoketone **11** (50.15, 235 mmol), ethylene glycol (80.5 g, 1.34 mol) and *p*-toluene sulphonic acid (2.15 g, 11 mmol) in 350 mL toluene was stirred under refluxing with Dean Stark apparatus over night during which period the water produced was distilled off as the toluene azeotrope. Reaction solvent was removed in *vacuo* and the residue was dissolved in 250 mL DCM. The solution was then washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4,

evaporated in *vacuo* to give the crude 2-(1-bromoethyl)-2-phenyl-1,3-dioxolane **12** (53.2 g, 88%). This compound was used as obtained for the next elimination step. TLC R*f*:0.40 [hexane]; ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.59 (3H, d, *J*=6.8), 3.82–3.91 (2H,m), 4.13–4.20 (2H,m), 4.38 (1H, q, *J*=6.8), 7.32–7.38 (3H, m, Ar-H), 7.49–7.52 (2H, m, Ar-H).

2-phenyl-2-vinyl-1,3-dioxolane 13[8]

Application of the elimination procedure for synthesis of **7** to bromo ketal **12** (67.1 g, 0.26 mol) and KOH (88.1 g, 1.57 mol) in 300 mL DMSO at 120°C for 3 hours gave the crude product. Purification by distillation afforded 2-phenyl-2-vinyl-1,3-dioxolane **13** (41.7 g, 91%) as a clear oil. b.p 133–135°C/15 mmHg, (Lit.[8] 59–60°C/0.3 mmHg);TLC, R*f*: 0,41 [hexane]; ^{1}H NMR H (400 MHz, $CDCl_3$) (ppm) 3.90–3.98 (2H, m), 4.02–4.09 (2H, m), 5.24 (1H, ddd, *J*=0.4, 1.6 and 10.4), 5.35 (1H, ddd, *J*=0.4, 1.2 and 17.2), 6.02 (1H, ddd, *J*=0.4, 10.4 and 17.2), 7.28–7.57 (3H, m, Ar-H), 7.48-7.52 (2H, m, Ar-H).

2-ethynyl-2-phenyl-1,3-dioxolane 15[8]

Application of the bromination procedure for synthesis of **8** to 2-phenyl-2-vinyl-1,3-dioxolane **13** (15.1 g, 85.8 mmol) in 100 mL DCM at -10 °C and bromine (12.3 g, 77 mmol) in 25 mL DCM produced the crude dibromide compound **14**. TLC, R*f*: 0.47 [hexane]. The compound was directly subjected to elimination step without purification or characterization.

Application of the elimination procedure for synthesis of **9** the crude dibromide **14** in 20 mL heptane, powdered KOH (24 g, 0.43 mol) and 18-crown-6 (250 mg) in 100 mL heptane gave the crude product. Purification by fractional distillation afforded 2-ethynyl-2-phenyl-1,3-dioxolane **15** (10.3 g, 70% over two steps) as a clear oil; b.p 110°C/15 mmHg, (Lit.[8], 92–96°C/0.6 mmHg); TLC, R*f*: 0.28 [hexane]; IR (film) υ_{max}/cm^{-1} 3281, 2109, 697 (HC≡C-); ^{1}H NMR (400

MHz, $CDCl_3$) (ppm) 2.70 (1H,s), 4.09–4.15 (2H, m), 4.21–4.27 (2H, m), 7.34–7.40 (3H, m, Ar-H), 7.68–7.73 (2H, m, Ar-H).

Synthesis of 2-ethynyl-2-methyl-1,3-dioxolane 20

2-(1-chloroethyl)-2-methyl-1,3-dioxolane 17[12]

A mixture of 3-choloro-2-butanone **16** (30.5 g, 278 mmol), ethylene glycol (16.5 g, 266 mmol) and *p*-toluene sulphonic acid (210 mg, 1.1 mmol) in 350 mL benzene was stirred under refluxing with Dean Stark apparatus over night during which period the water produced was distilled off as the toluene azeotrope. Reaction solvent was removed in *vacuo* and the residue was dissolved in 250 mL DCM. The solution was then washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, evaporated in *vacuo* to give the crude ketal **17**. Purification by distillation afforded 2-ethynyl-2-methyl-1,3-dioxolane **15** (36 g, 86%) as a pale yellow oil; b.p 55–58°C/15 mmHg, (Lit.[12], 58–60°C/ 20 mmHg); TLC, R*f*: 0.56 [EtOAc:hexane(1:10)];^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.43 (3H, s), 1.52 (3H, d, *J*=6.8), 3.95-4.05 (5H,m).

2-methyl-2-vinyl-1,3-dioxolane 18[12]

Application of the elimination procedure for synthesis of **7** to chloro ketal **17** (25 g, 166 mmol) and KOH (60 g, 1.07 mol) in 150 mL DMSO at 100°C for 3 hours gave the crude vinyl-1,3-dioxolane. Purification by distillation at atmospheric pressure afforded 2-methyl-2-vinyl-1,3-dioxolane **18 (**15.7 g, 83% yield) as a clear oil. b.p 112–114°C, (Lit.[12], 110–112°C); TLC, R*f*: 0.54 [EtOAc:hexane (1:6)]; ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.47 (3H, s), 3.86–4.02 (4H, m), 5.14 (1H, dd, *J*=1.6 and 10.8), 5.37 (1H, dd, *J*=1.6 and 17.2), 5.79 (1H, dd, *J*=10.4 and 17.2).

2-ethynyl-2-methyl-1,3-dioxolane 20[10]

Application of the bromination procedure for synthesis of **8** to 2-methyl-2-vinyl-1,3-dioxolane **18** (18.1 g, 159 mmol) in 150 mL DCM at –10°C and bromine (22.9 g, 143 mmol) in 30 mL DCM produced the crude dibromide compound **19**. TLC, R*f*: 0.44 [EtOAc:hexane (1:6)].The compound was directly subjected to elimination step.

Application of the elimination procedure for synthesis of **9** to the crude dibromide **19** in 30 mL *n*-dodecane, powdered KOH (44.5g, 0.8 mol) and 18-crown-6 (0.7 g) in 130 mL *n*-dodecane, gave the crude product. Purification by distillation at atmospheric pressure afforded 2-ethynyl-2-methyl-1,3-dioxolane **20** (10.7 g, 60% over two steps) as a clear oil; b.p 125°C, (Lit[10b], 44°C/38 mmHg); TLC, R*f*: 0.59 [EtOAc:hexane (1:6)]. IR (film) υ_{max}/cm^{-1}; 3277, 2112, 660 (HC≡C-); ^{1}H NMR (400 MHz, $CDCl_3$) (ppm) 1.69 (3H, d, J=2), 2.47 (1H, s), 3.97-4.10 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) (ppm) 26.10, 64.61 (2xC), 70.94, 82.05, 100.34.

Nucleophilic substitution of 1,2-cyclic sulfamidate 21 with acetylides 22 and 25

Synthesis of (S)-ethyl-5-(benzylamino)-6-phenyl-hex-2-ynoate 24[13]

To a solution of triethylorthopropiolate (1.35 g, 7.85 mmol) in 30 mL freshly distilled dry THF under argon atmosphere, cooled at –10°C over ice-salt bath was added dropwise *n*-butyllithium (5.0 mL, 7.9 mmol, 15% solution in hexane) and the solution was stirred at this temperature for 1 h. A solution of phenylalaninol 1,2- cyclic sulfamidate **21** (1.2 g, 3.96 mmol) in 3 mL dry THF was then added to the resulting acetylide solution via a syringe. After stirring at –10ºC for 5–6 h, the reaction mixture was allowed to warm up to room temperature gradually with stirring overnight (24 h). TLC monitoring showed complete consumption of **21**. The resulting mixture was then treated with 3 mL 5M HCl solution to hydrolyze the *N*-sulfate intermediate for 3 h before neutralization with saturated $NaHCO_3$ solution. Extraction with ether (3x50 Ml) and

drying over anhydrous Na_2SO_4 followed by evaporation of volatiles in *vacuo* gave the crude product. Purification by column chromatography using [EtOAc: Hexane (1:8) to (1:3) gradient] solvent systems (containing 0.5% triethylamine) afforded (*S*)-ethyl-5-(benzylamino)-6-phenyl-hex-2-ynoate **24** as a pale yellow oil (1110 mg, 89% yield). TLC, R*f*: 0.53 [(EtOAc:Hexane) 1:3]; $[\alpha]_D^{31}$ –6.4 (*c* 1.95, $CHCl_3$); IR (film); υ_{max}/cm^{-1}; 3481,3338 (NH), 2337 (C≡C), 1706 (C=O ester); ^1H NMR δ_H (400 MHz, $CDCl_3$) (ppm) 1.32 (3H, t, *J*=7.2), 2.40-2.51 (2H, m), 2.81-2.90 (2H, m), 3.02-3.08 8 (1H, m), 3.77 (1H, d, *J*=13.6), 3.86 (1H, d, *J*=13.6), 4.23 (2H, q, *J*=7.2), 7.16-7.31 (10H, m, Ar-H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) (ppm) 14.27, 23.73, 40.61, 51.27, 56.74, 62.07, 75.52, 85.59, 126.76, 127.24, 128.22, 128.64, 128.77, 129.53, 138.41, 140.08, 153.84; ESI-Tof (m/z): $[M+H]^+$ found 328.1809, $C_{21}H_{24}NO_2$ requires 328.1807.

Synthesis of (S)-N-benzyl-1-phenyl-5-(2-phenyl-1,3-dioxolan-2-yl)pent-4-yn-2-amine 27a

To a solution of phenyl ketal alkyne **15** (348 mg, 2 mmol) in 10 mL freshly distilled dry THF under argon atmosphere, cooled at –10°C over ice-salt bath was added dropwise *n*-butyllithium (1.4 mL, 2.2 mmol, 15% solution in hexane) and the solution was stirred at this temperature for 1 h. A solution of phenylalaninol 1,2- cyclic sulfamidate **21** (303 mg, 1 mmol) in 3 mL dry THF was then added to the resulting acetylide solution via a syringe. After stirring at –10ºC for 5-6 h, the reaction mixture was allowed to warm up to room temperature gradually with stirring overnight (24 h). TLC monitoring showed complete consumption of **21**. The resulting mixture was then added one drop conc. H_2SO_4 and one drop H_2O sequentially (total 4 drops H_2SO_4 and 4 drops H_2O) with stirring for 2h to hydrolyze the *N*-sulfate intermediate before neutralization with saturated $NaHCO_3$ solution. Extraction with ether (3 × 20mL) and drying over anhydrous

Na_2SO_4 followed by evaporation of volatiles in *vacuo* gave the crude product. Purification by column chromatography using [EtOAc: Hexane (1:7) to (1:4) gradient] solvent systems (containing 0.5% triethylamine) afforded (*S*)-*N*-benzyl-1-phenyl-5-(2-phenyl-1,3-dioxolan-2-yl)pent-4-yn-2-amine **27a 27a** as a pale yellow oil (358mg, 90% yield). TLC, R*f*: 0.42 [(EtOAc:hexane) 1:3]; $[\alpha]_D^{30}$ +0.36 (*c* 6.0, $CHCl_3$); IR (film); υ_{max}/cm^{-1}; 3357 (NH), 2234 (C≡C); ^1H NMR δ_H (400 MHz, $CDCl_3$) (ppm) 2.40 (1H, dd, *J*=5.6 and 16.8), 2.47 (1H, dd, *J*=6.0 and 16.8), 2.83 (1H, dd, *J*=7.2 and 13.6), 2.89 (1H, dd, *J*=6.0 and 13.6), 3.01–3.07 (1H, m), 3.79 (1H, d, *J*=13.2), 3.88 (1H, d, *J*=13.2), 4.12–4.18 (2H, m), 4.22–4.28 (2H, m), 7.17–7.42 (13H, m, Ar-H), 7.73–7.77 (2H, m, Ar-H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) (ppm) 23.50, 40.48, 51.14, 57.14, 65.09, 80.61, 84.20, 102.45, 125.87, 126.37, 126.90, 127.98, 128.22, 129.10, 138.70, 139.50, 140.23; LC/MS Q-TOF (m/z): $[M+H]^+$ found 398.2116, $C_{27}H_{28}NO_2$ requires 398.2120.

Synthesis of (S)-N-benzyl-5-(2-methyl-1,3-dioxolan-2-yl)-1-phenylpent-4-yn-2-amine 27b

To a solution of methyl ketal alkyne **20** (225 mg, 2 mmol) in 10 mL freshly distilled dry THF under argon atmosphere, cooled at -10 °C over ice-salt bath was added dropwise *n*-butyllithium (1.3 mL, 2.1 mmol, 15% solution in hexane) and the solution was stirred at this temperature for 1 h. A solution of phenylalaninol 1,2- cyclic sulfamidate **21** (303 mg, 1 mmol) in 3 mL dry THF was then added to the resulting acetylide solution via a syringe. After stirring at –10ºC for 5–6 h, the reaction mixture was allowed to warm up to room temperature gradually with stirring overnight (24 h). TLC monitoring showed complete consumption of **21**. The resulting mixture was then added one drop conc. H_2SO_4 and one drop H_2O sequentially (total 4 drops H_2SO_4 and 4 drops H_2O) with stirring for 2h to hydrolyze the *N*-sulfate intermediate before neutralization

with saturated $NaHCO_3$ solution. Extraction with ether (3 × 20 mL) and drying over anhydrous Na_2SO_4 followed by evaporation of volatiles in *vacuo* gave the crude product. Purification by column chromatography using [EtOAc: Hexane (1:6) to (1:2) gradient] solvent systems (containing 0.5% triethylamine) afforded (*S*)-*N*-benzyl-5-(2-methyl-1,3-dioxolan-2-yl)-1-phenylpent-4-yn-2-amine **27b** as a pale yellow oil (306mg, 91% yield). TLC, R*f*: 0.22 [(EtOAc:Hexane) 1:3]; $[\alpha]_D^{24}$ –5.5 (*c* 2, $CHCl_3$); IR (film); υ_{max}/cm^{-1}; 3330 (NH), 2241 (C≡C); ^1H NMR δ_H (400 MHz, $CDCl_3$) (ppm) 1.72 (3H, s), 2.34 (2H, ddd, *J*=5.6, 16.8 and 20.6), 2.83 (2H, dd, *J*=7.2 and 13.6), 2.95–3.01 (1H, m), 3.78 (1H, d, *J*=13.2), 3.86 (1H, d, *J*=13.2), 3.96–4.02 (2H, m), 4.03–4.10 (2H, m), 7.17–7.32 (10H, m, Ar-H); ^{13}C NMR δ_C (100 MHz, $CDCl_3$) (ppm) 26.68, 40.38, 51.11, 57.01, 64.59, 80.86, 81.34, 100.86, 126.38, 126.95, 127.99, 128.41, 128.47, 129.34, 138.70, 140.23; LC/MS Q-TOF (m/z): $[M+H]^+$ found 336.1957, $C_{22}H_{26}NO_2$ requires 336.1964.

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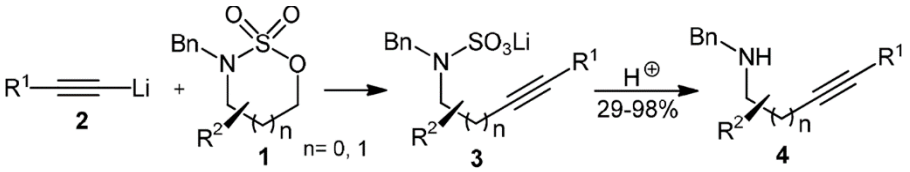
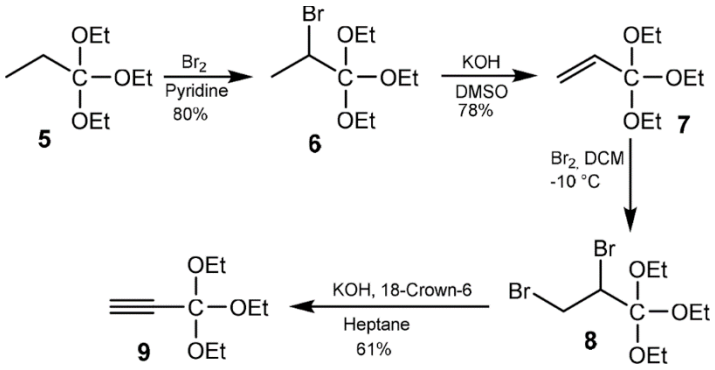
Scheme 1. Nucleophilic substitution of cyclic sulfamidates with acetylides.



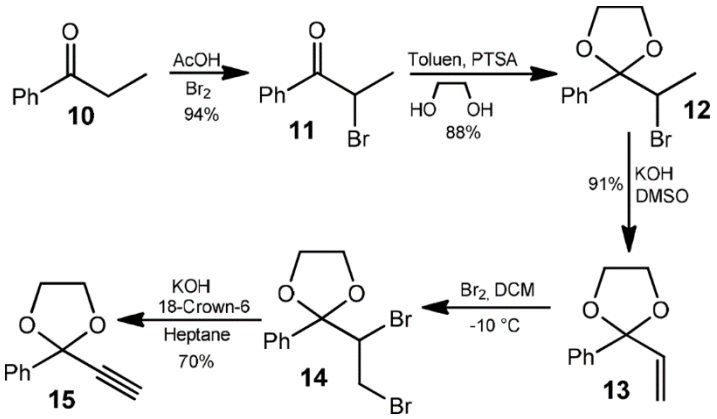
1,2-cyclic sulfamidate (n=0)

1,3-cyclic sulfamidate (n=1)

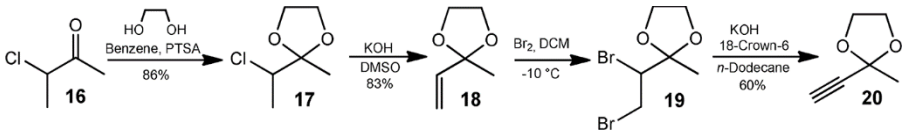
Scheme 2. Synthesis of 3,3,3-triethoxypropyne **9**.



Scheme 3. Synthesis of 2-ethynyl-2-phenyl-1,3-dioxolane **15**.



Scheme 4. Synthesis of 2-ethynyl-2-methyl-1,3-dioxolane **20**.



Scheme 5. Nucleophilic substitution of 1,2-cyclic sulfamidate **21** with acetylides **22** and **25**.