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Practical one-step synthesis of ethynylglycine synthon from Garner's aldehyde

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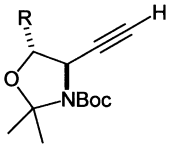
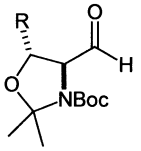
Abstract—A simple, efficient and practical synthesis of (*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine (ethynylglycine synthon) is described. The method involves in situ formation of dimethyl 1-diazo-2-oxopropyl phosphonate from dimethyl 2-oxopropyl phosphonate and 4-acetamidobenzene sulfonyl azide and one-pot reaction on Garner's aldehyde. The reaction has been extended to other aminoaldehydes.

1. Introduction

(*R*)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyl-oxazolidine **1a** (ethynylglycine synthon) is a valuable chiral synthon. It is easily functionalized: alkylation or acylation under basic conditions,[1] oxidative homocoupling by CuCl,[2] palladium catalysed couplings,[3] hydrostannylation followed by Stille couplings,[3a] stannylcupration,[3c] silylcupration,[4] cycloaddition,[5] have been recently reported.

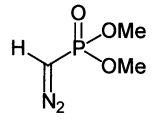


1a : R=H
1b : R=Me



2a : R=H
2b : R=Me

This compound has been prepared from Garner's aldehyde **2a**[6] either by a two steps sequence via dibromovinyl intermediate (Corey–Fuchs strategy)[1a,3b,3c,5,7] (60–80% yield from **2a**) or via direct aldehyde-to-alkyne one-carbon homologation (diazo strategy).[1b,1d,2,3a,8] This latter transformation is known to be milder and compatible with sensitive functionalities[1b,9,10] and implies the preparation of the diazophosphonates **3** (Seyferth–Colvin–Gilbert reagent)[11] or **4** (Ohira reagent).[12,13] Synthesis of diazophosphonate **3** is lengthy (five steps starting from phthalimide) and the yield of the final step including the vaccum distillation is not satisfactory. Moreover, this compound presents stability problems and conversion to the alkyne using compound **3** requires stronger reaction conditions (*t*-BuOK, −78°C, THF). On the other hand, dimethyl 1-diazo-2-oxopropyl phosphonate **4** is easier to prepare[14] and alkyne formation (K_2CO_3, rt, MeOH)[12] avoids the use of strong bases, low temperature and tolerates various functional groups.[15] Using diazophosphonate **3**, we obtained alkyne **1a** in 60% yield[1b] while using **4** we and others obtained yields ranging 75–80%.[1b,1d,2,3a,8b]



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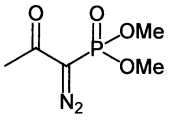

4

Ohira reagent **4** is usually prepared in 80–90% yield according to the literature by reaction of dimethyl 2-oxopropyl phosphonate **5** and potentially explosive tosyl azide (TsN_3) using NaH in benzene followed by chromatographic purification.[10,14]

In an attempt to increase the simplicity, efficiency and safety of the method, we now report that Garner's aldehyde **2a** and the threonine derivative **2b** can be transformed in good yields to the ethynyloxazolidines **1a** and **1b**, respectively, using a safe and efficient one-pot multicomponent process.

2. Results and discussion

The method involves in situ formation of dimethyl 1-diazo-2-oxopropyl phosphonate **4** from commercially available dimethyl 2-oxopropyl phosphonate **5** and

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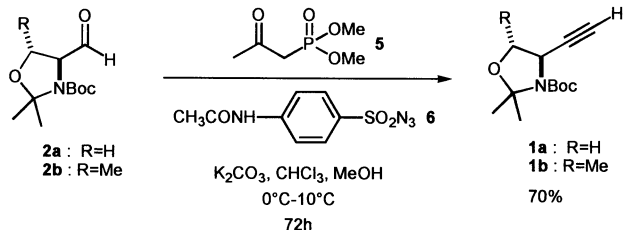
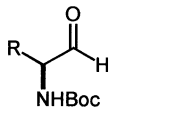


Scheme 1.

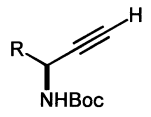
4-acetamidobenzene sulfonyl azide **6** and clean one-pot reaction of this intermediate on aldehydes **2** (Scheme 1).[16]

Chloroform was chosen as solvent in the diazophosphonate formation stage because the sulfonamide formed in the reaction is not soluble in this solvent, decreasing the possible reaction with the aldehyde in the second stage of the reaction.[17] However, filtering sulfonamide before addition of the aldehyde did not increase the yield. Performing the reaction at 40–50°C diminishes reaction time (yield is not affected) but leads to some loss of enantiopurity as observed by optical rotation measurements. Although the reaction seems to be slower with 4-acetamidobenzene sulfonyl azide **6** comparing to TsN_3, the former was prefered as diazo transfert reagent. Being a crystalline solid, it is more convenient to manipulate, is easier to prepare in a pure form and is known to not exhibit impact properties.[18] In fact, preparation of TsN_3 when performed in ethanol[19] lead to the contamination of product with up to 5% (^{1}H NMR) of ethyl 4-toluene sulfonate.

The reaction has also been extended to two other α-amino aldehydes **2c** and **2d** derived from natural occurring phenylalanine and leucine, leading to the corresponding propargylic amines **1c** and **1d**, respectively. The latter compound has been for the first time fully characterized. In both cases, aldehydes were completely converted into the corresponding propargylamines which were recovered in 40% yield after flash chromatography. Parallel experiments showed that yields of final compounds are similar when the present one-pot procedure is used instead of isolated diazophosphonate **4**. The enantiomeric purity of unprecedently reported compound **1d** was established as 92% by ^{1}H NMR analysis of the diastereomeric Mosher amides prepared by reaction of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl choride (MTPACl) with the primary amine in turn obtained by removal of the Boc protective group in the presence of Me_3SiI.



2c : R=$C_6H_5CH_2$-
2d : R=$(CH_3)_2CHCH_2$-



1c : R=$C_6H_5CH_2$-
1d : R=$(CH_3)_2CHCH_2$-

3. Conclusions

This procedure constitutes an expedious route to alkynes **1ab** from aldehydes **2ab** in good yields (70%) with no loss of optical purity as determined by optical rotations and comparison with literature values. It has been extended to two other α-amino aldehydes **2cd** in yields comparable with the classical method using prepared diazophosphonate **4** (40%) and with good enantiomeric purity as determined by NMR analysis of Mosher's derivatives. It offers the advantage of low cost, safety, ease of manipulation and could be good way for parallel synthesis.

4. Experimental

4.1. General

All solvents and reagents were used as purchased. Aldehydes **2** are commercially available or are easily synthesized following literature procedures.[6] 4-Acetamidobenzene sulfonyl azide **6** was prepared according to the literature.[18a,c] Purifications by flash column chromatography were performed using silica gel 60, 0.04–0.063 mm (230–400 Mesh) (Merck re: 9385), and TLC using silica gel 60F254, layer thickness 0.2 mm on aluminum sheets. Optical rotation were measured on a Perkin–Elmer 241 polarimeter in a 1 cm cell. IR spectra were obtained using a Nicolet 205 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 200 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane.

Caution: although 4-acetamido benzenesulfonyl azide exhibited no impact properties, proper caution should be exercised with all azide compounds.

4.2. General procedure for the preparation of alkynes 1 from aldehydes 2

In a three-necked round bottomed flask equiped with argon inlet and outlet and a pressure equalizing dropping funnel are placed dimethyl 2-oxopropylphosphonate **5** (538 mg, 3.2 mmol, 3.4 equiv.) in $CHCl_3$ (8 mL) under an argon atmosphere. The mixture is efficiently stirred under argon at 0°C (ice bath). 4-Acetamido benzene sulfonyl azide **6** (771 mg, 3.2 mmol, 3.4 equiv.) and K_2CO_3 (453 mg, 3.3 mmol, 3.5 equiv.) are added in one portion. The mixture is efficiently stirred under argon in an ice-water bath (temperature <10°C) for 48 h (TLC analysis indicates the reaction is complete). A fine white suspension is formed. K_2CO_3 (210 mg, 1.5 mmol, 1.6 equiv.) is added to the reaction mixture and a solution of aldehyde **2** (0.95 mmol) in MeOH (8 mL) is added dropwise (slow addition) to the reaction mixture, under argon, at 0°C (ice bath). The reaction mixture becomes thick-yellow. After 24 h in an ice-water bath (maximum temperature: 10°C), TLC examination shows that the reaction is finished. Saturated aq. NH_4Cl solution (25 mL) is added. The biphasic solution obtained is filtered in a separatory funnel. The organic phase is washed with a sat. aq. NH_4Cl solution (25 mL) then with water (2×25 mL). Each aqueous phase is extracted with $CHCl_3$ (10 mL). The combined organic phase is dried over Na_2SO_4 and evaporated. Crude product is purified by silica gel flash chromatography (10 g, diameter 20 mm, cyclohexane/ethyle acetate 95/5) to obtained pure alkyne **1** as a clear oil.

4.2.1. (*R*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyl-oxazolidine 1a. Yield: 154 mg (72%),[20] $[\alpha]_D^{20}=-99°$ (*c* 0.96, $CHCl_3$). [lit.[1b] $[\alpha]_D^{20}=-96.5°$ (*c* 1.23, $CHCl_3$), lit.[3a] $[\alpha]_D^{20}=-81.3°$ (*c* 2.43, $CHCl_3$), lit.[1d] $[\alpha]_D^{20}=-88.2°$ (*c* 1.05, $CHCl_3$), lit.[3c] $[\alpha]_D^{20}=-73.5°$ (*c* 1.01, $CHCl_3$)]. No loss of optical purity was observed as determined by optical rotations measurements of **1a** and *ent*-**1a** (see below).

Alkyne **1a** has been fully characterised previously by us and others and our present data are consistent with those reported before.[1b,3c]

4.2.2. (*S*)-2,2-Dimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyl-oxazolidine (*ent*-1a). This was synthesized from *ent*-**2a** on 10 mmol scale using the same procedure. Yield: 1.55 g (69%), $[\alpha]_D^{20}=+102°$ (*c* 1.02, $CHCl_3$).

4.2.3. (*R*,*R*)-2,2,5-Trimethyl-3-(*tert*-butoxycarbonyl)-4-ethynyloxazolidine 1b. This was synthesized from **2b** on 1 mmol scale using the same procedure. Yield: 162 mg (69%), $[\alpha]_D^{20}=-93.1°$ (*c* 1.06, $CHCl_3$). In the case of this aldehyde, a longer reaction time (72 h) for second stage may be needed. IR (neat): 2100, 3255 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): 1.35 (d, 3H, *J*=6.0 Hz, C*H*$_3$CHO), 1.48 (s, 9H, Boc), 1.52, 1.57 (2s, 6H, 2CH_3), 2.32 (bs, 1H, CCH), 3.97 (m, 1H, CHN), 4.19 (dq, 1H, *J*=6.0, 7.3 Hz, CH_3C*H*O); ^{13}C NMR (50.3 MHz, $CDCl_3$): 18.1 (*C*H_3CHO), 24.9, 26.7 ((*C*H_3)$_2$CON), 28.2 ((*C*H_3)$_3$C), 54.4 (CHN), 71.4 (C*C*H), 76.1 (CHO), 80.3, 82.0 ((CH$_3$)$_3$*C*), *C*CH), 94.5 ((CH$_3$)$_2$*C*ON), 151.5 (NCO_2); MS (DCI, NH_3): 257 $(M+NH_4)^+$, 240 $(M+H)^+$, 201 $(M-CH_2C(CH_3)_2+NH_4)^+$, 184 $(M-CH_2C(CH_3)_2+H)^+$.

4.2.4. (*S*)-1-Benzyl-*N*-(*tert*-butoxycarbonyl)-2-propynamine 1c. This was synthesized from **2c** on 1 mmol scale using the same procedure. Yield: 66 mg (45%), $[\alpha]_D^{20}=-10.1°$ (*c* 0.96, $CHCl_3$). [lit.[21] $[\alpha]_D^{20}=-10.6°$ (*c* 1.01, $CHCl_3$)]. Alkyne **1c** has been fully characterized previously by us and our present data are consistent with those reported before.[21]

4.2.5. (*S*)-1-Methylpropyl-*N*-(*tert*-butoxycarbonyl)-2-propynamine 1d. This was synthesized from **2d** on 1 mmol scale using the same procedure. Yield: 99 mg (42%), $[\alpha]_D^{20}=-42.6°$ (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): 3445, 3307, 2251; ^1H NMR (200 MHz, $CDCl_3$): 0.93 (d, 3H, *J*=6.6 Hz, CH_3), 0.94 (d, 3H, *J*=6.6 Hz, CH_3), 1.45 (s, 9H, Boc), 1.85–1.25 (m, 1H+2H, $CHCH_2$), 2.25 (d, 1H, *J*=2.2 Hz, CCH), 4.40–4.20 (m, 1H, CHN), 4.70 (bs, 1H, NH); ^{13}C NMR (50.3 MHz, $CDCl_3$): 21.8 (CH_3), 22.6 (CH_3), 24.8 (CH_2), 28.2 (C(*C*H_3)$_3$), 41.2 (CHN), 45.1 (*C*H(CH$_3$)$_2$); 70.7 (C+*C*H), 77.6 (*C*(CH$_3$)$_3$), 83.8 (*C*CH), 154.7 (NCO_2); MS (EI): 155 $(M-CH_2C(CH_3)_2)^+$, 57 $(t\text{Bu})^+$.

4.2.6. Synthesis of the Mosher's amide of compound 1d. Compound **1d** (0.1 mmol) was dissolved in $CHCl_3$ and stirred with Me_3SiI (0.12 mmol) for 10 min. After dilution in methanol and evaporation of the solvent, the deprotected amine was dissolved in CCl_4 (1 mL) and reacted with (*S*)-(+)-MTPACl and pyridine for 48 h. After workup and evaporation of the solvent the crude was analyzed by ^1H NMR and the enantiomeric excess determined as 92%. ^1H NMR (200 MHz, $CDCl_3$): (*S*,*S*): 3.43 (q, 3H, J_{H-F}=1.3 Hz, OCH_3) (major diastereoisomer); (*R*,*S*): 3.46 (q, 3H, J_{H-F}=1.3 Hz, OCH_3) (minor diastereoisomer).

4.2.7. Dimethyl 1-diazo-2-oxopropyl phosphonate 4. To a solution of phosphonate **5** (332 mg, 2 mmol) and TsN_3 (394 mg, 2 mmol) in acetonitrile (5 mL) at 0°C is added K_2CO_3 (276 mg, 2 mmol). The mixture is left under stirring at 0°C to rt for 5 h. TLC analysis shows that reaction is complete. The mixture is evaporated to dryness, triturated in $CHCl_3$ and 4-toluene sulfonamide is filtered off. Evaporation of the solvent leaves crude diazophosphonate **4** as an oil (332 mg, 86%). ^1H NMR analysis is consistent with the structure of **4** contaminated with 4-toluene sulfonamide. Crude **4** is purified by flash chromatography on silica gel as described in the literature.[14]

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