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A facile synthesis of 4-methylene-1,3-oxazolidines from γ-hydroxybutynoate and *N*-tosylimines

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ABSTRACT

Both nucleophilic and basic catalysts have been used to promote the cyclization reactions between γ-hydroxybutynoate and *N*-tosylimines to afford 4-methylene-1,3-oxazolidines in good yields. *E*- and *Z*-isomers of the final products have been isolated and characterized by NMR spectroscopy and X-ray data.

A number of literature reports highlight the catalytic generation of strong bases by addition of nucleophilic phosphines to electron-deficient unsaturated substrates.[1] The thus formed zwitterionic phosphonium salts are basic enough to deprotonate a variety of carbon based[2] and heteroatomic[3] pronucleophiles including alcohols,[4] and therefore initiate simple or multicomponent additions as well as cyclization processes (Fig. 1).

Among others, bifunctional substrates such as activated alkynes bearing alcohol groups, have been used in organocatalytic processes of this class in which the alcohol function behaves as the pronucleophilic group.[5] A recent relevant example from Williamson, typifies this strategy (Scheme 1).[6] In this case, an alcoholate function is generated by addition of a nucleophilic phosphine to ethyl γ-hydroxy-2-butynoate and subsequent proton exchange reaction. The alcoholate adds then to highly activated electrophilic olefins to afford methylenetetrahydrofurans, via formal [3+2] annulations.[7]

As a complement to this recent Letter we report herein on the analogous reaction of methyl γ-hydroxy-2-butynoate **1** with *N*-tosylimines **2** promoted by phosphine catalysts. We also show that the same cyclizations can be alternatively performed in the presence of inorganic bases.

During investigations into enantioselective phosphine-promoted [3+2] cyclizations between alkynyl or allenic esters and imines,[8] we noticed that PBu_3 induces a clean reaction between methyl 4-hydroxybutynoate **1** and *N*-tosylbenzaldimine, however none of the expected 3-pyrroline was obtained. At room temperature, in the presence of a 10 mol % amount of phosphine, the reaction of the activated propargylic alcohol **1** with *N*-tosyl-benzaldimine **2a** afforded indeed 4-methylene-1,3-oxazolidine **3a** as the unique reaction product (Scheme 2).[9]

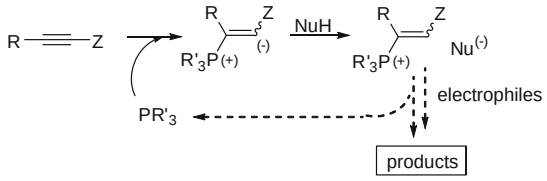
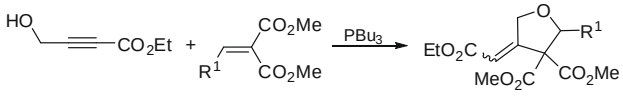
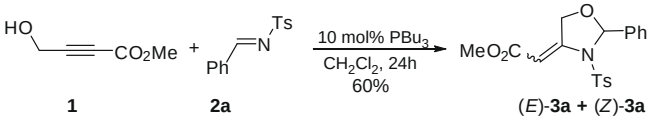


Figure 1. Organocatalytic generation of strong bases by addition of nucleophilic phosphines to unsaturated substrates (umpolung process).



Scheme 1. Phosphine-promoted synthesis of methylenetetrahydrofurans.[6]



Scheme 2. Phosphine-promoted cyclization between γ-hydroxybutynoate and *N*-tosylbenzaldimine.

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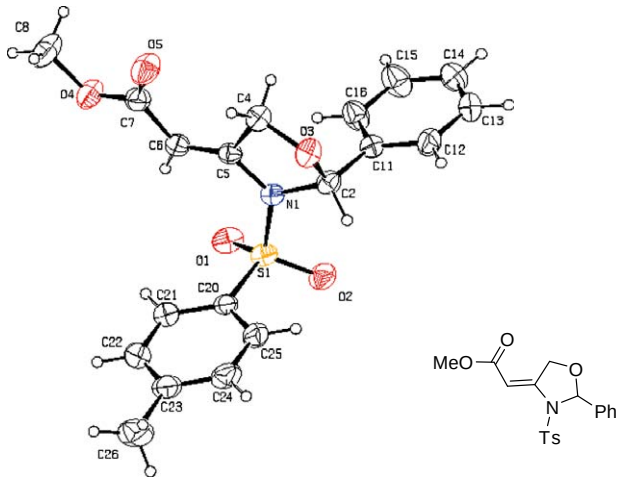
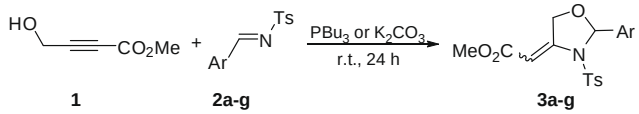


Figure 2. ORTEP drawing of the 4-methylene-1,3-oxazoline (*E*)-**3a**.

Table 1
Synthesis of 4-methylene-1,3-oxazolidines from γ-hydroxy-butynoate and *N*-tosylimines



1 2a-g 3a-g

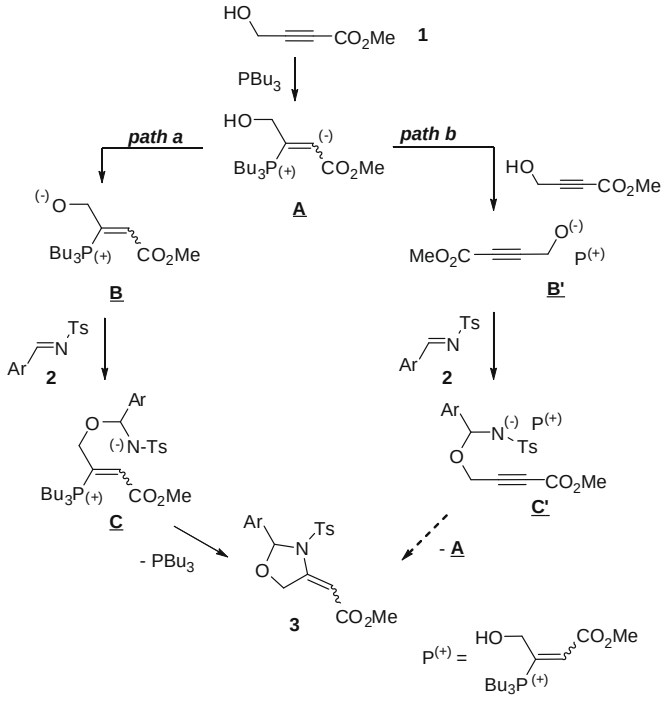
	Ar		PBu_3 Yield[a] (%)	PBu_3 *E*:*Z*	K_2CO_3 Yield[b] (%)	K_2CO_3 *E*:*Z*
1	Ph	**3a**	60	54:46[c]	91	62:38
2	1-Naphthyl	**3b**	60	57:43	98	60:40
3	CH=CH–Ph	**3c**	78	56:44	94	72:28
4	*p*-NO_2–C_6H_4	**3d**	95	60:40	91	66:34
5	*p*-CF_3–C_6H_4	**3e**	55	66:34	64	65:35
6	*o*-Me–C_6H_4	**3f**	60	60:40	88	70:30
7	*p*-MeO–C_6H_4	**3g**	<5	—	86	67:33

[a] Reactions performed in CH_2Cl_2 with a 10% amount of PBu_3.
[b] Reactions performed in ether at rt with a 20% amount of K_2CO_3.
[c] A 65:35 *E*/*Z* ratio was obtained when the reaction was performed in ether.

The cyclization product was obtained in 60% isolated yield, as a mixture of *E*- and *Z*-isomers in a 54/46 ratio. The isomers were easily separated by column chromatography on silica gel and fully characterized.[10] The structural assignment and the stereochemistry of the double bond were unambiguously proved by X-ray diffraction study of the *E*-isomer of **3a**. The ORTEP drawing is shown in Figure 2.

As far as we know, 4-methylene-1,3-oxazolidines have been barely mentioned in the literature.[11] 2-Aryl-substituted oxazolidines of this class have been reported only by Lhommet et al.[11a] They have been obtained by reacting methyl hydroxybutynoate with *N*-(1-phenylethyl)imines in refluxing toluene, in the presence of hydroquinone. Thus, reaction shown in Scheme 2 affords an alternative protocol in which phosphine-organocatalysis is applied to promote these cyclizations under very mild conditions.

Two possible mechanisms for the cyclization reaction are shown in Scheme 3. As the first step, both pathways involve addition of PBu_3 to **1** to give the phosphonium salt **A**. This is followed by a proton exchange between the carbanionic moiety of **A** and an hydroxyl function in either an intramolecular (*path a*) or an intermolecular process (*path b*). The alcoholate **B** (or **B′**) adds then to the imine and, finally, an intramolecular Michael reaction gives oxazolidine **3**, while regenerating the phosphine catalyst (or the key intermediate **A**).



Scheme 3. Proposed key steps for the formation of **3**.

Since the postulated role of the phosphine is primarily to generate a strong base, it is expected that the same cyclization reaction **A** might take place in the presence of other organic or inorganic bases. Oxazolidines **3a** have been obtained indeed in good yields by reacting **1** and **2** in the presence of either catalytic amounts of DMAP (64% yield under the reaction conditions of Scheme 2) or K_2CO_3 (in ether at room temperature, 91% yield). In the absence of bases, no reaction is observed under the conditions mentioned above. Phosphines such as PPh_3 or P(*i*Bu)$_3$ are inactive, which likely relates to their lower nucleophilic character, compared to PBu_3.

The scope of the reaction has been demonstrated by variations of the imine substituent, as shown in Table 1.

Starting from several *N*-tosylimines, the use of K_2CO_3 as the base gives oxazolidines in uniformly high yields. For phosphine-promoted reactions, conversion rates are somewhat lower and higher substrate dependence is observed, with isolated yields of between 55% and 95%. The electron-rich *p*-MeO-benzaldimine failed to react in the presence of phosphine. Oxazolidines **3a–f** were formed as mixtures of the (*E*)- and (*Z*)-isomers in about 60:40 ratios, with only small differences being observed between the two catalytic systems. Both isomers can be obtained separately by chromatography on silica gel and ^{1}H NMR data allow reliable assignments of their respective *E*/*Z* stereochemistry. For instance, the CH_2 moieties display typical chemical shifts at $\delta = 4.8–4.9$ and 4.1–4.2 ppm for the *E*- and *Z*-isomers, respectively.

A few attempts have been made using chiral phosphines as nucleophilic catalysts with the aim of setting enantioselective processes. Electron-rich phosphines such as (*S*)-*t*-Bu-Binepine[12] and (*S,S*)-Cy-FerroPHANE[13] displayed good conversion rates, but the enantiomeric excesses were lower than 10%.[14]

In summary, the synthetic protocol reported here represents a rapid and efficient access to 4-methylene-1,3-oxazolines, a rarely described heterocyclic platform. The methyleneoxazolines **3** display interesting chemical features and functionalities and might serve as suitable precursors to a variety of nitrogen-containing compounds including β-substituted-β-aminoalcohols and the corresponding acids. The use of inorganic bases as catalysts is likely to represent the easiest and most convenient approach to oxazolidines **3** in racemic form, while the use of suitable chiral nucleophiles might open the way to enantiomerically enriched species.

Supplementary data

Experimental procedures and spectral data for compounds **3a**–**g**. X-ray crystal structure determination for (*E*)-**3a**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.009.

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9. A 10 mol % amount of tributylphosphine (50 μL, 1 M solution in toluene) was added to a solution of methyl 4-hydroxybut-2-ynoate (57 mg, 0.5 mmol) and *N*-tosylimine **2a** (0.5 mmol) in anhydrous CH_2Cl_2 (2 mL) under argon atmosphere. The resulting mixture was stirred at room temperature for 24 h and the solvents were removed. The crude product was purified by TLC on silica gel plates (heptane/ethyl acetate, 7/3 mixture) to give the pure *Z*- and *E*-isomers of the final oxazolidine **3a**. No defined by-products have been isolated from these reactions.
10. *Compounds (E)-***3a** *and (Z)-***3a** *were separated by TLC on silica gel with a heptane/ethyl acetate 7/3 mixture as the eluent*. (*E*)-**3a**: R_f = 0.33; white solid (mp = 117–120 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 3.69 (s, 3H), 4.94 (dd, *J* = 15.6 Hz, *J* = 1.8 Hz, 1H), 4.99 (dd, *J* = 15.6 Hz, *J* = 1.8 Hz, 1H), 6.11 (t, *J* = 1.8 Hz, 1H), 6.53 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.35–7.42 (m, 3H), 7.43–7.50 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 51.5, 70.9, 94.2, 95.9, 127.0, 127.7, 128.8, 129.6, 130.1, 134.7, 137.3, 145.5, 151.5, 167.5 ppm. Anal. Calcd for $C_{19}H_{19}NO_5S$: C, 61.11; H, 5.13; N, 3.75. Found: C, 61.17; H, 5.07; N, 3.51. (*Z*)-**3a**. R_f = 0.22; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.87 (s, 3H), 4.15 (d, *J* = 13.5 Hz, 1H), 4.19 (d, *J* = 13.5 Hz, 1H), 5.58 (s, 1H), 6.52 (s, 1H), 7.30–7.40 (m, 5H), 7.53 (d, *J* = 8 Hz, 2H), 7.79 (d, *J* = 8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 52.1, 68.2, 94.1, 106.6, 126.7, 128.1, 128.8, 129.3, 130.0, 135.1, 136.8, 144.1, 145.1, 166.0 ppm.
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14. Racemization of the stereogenic carbon of **3a** due to the basic reaction conditions cannot be ruled out.