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THE SYNTHESIS OF ISOXAZOLES FROM β,γ-ACETYLENIC OXIMES

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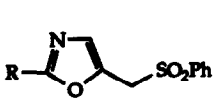
Abstract: β,γ-Acetylenic oximes (prepared from α-bromooximes) undergo facile conversion to 3,5-disubstituted isoxazoles on mild base treatment.

We have described the synthesis of oxazoles (1) from appropriately functionalized allylic amides and carbamates via an intramolecular addition-elimination strategy[2]. Others[3] have demonstrated that base-catalyzed cyclization of N-acylpropargylamines yield oxazoles. The cyclization chemistry of various N-functionalized propargylamines has been explored as well[4]. Interestingly, there are but a few examples of propargyloximes (2) and little is known of their chemistry[5]. We report herein a mild, base-promoted method to cyclize propargyloximes to form isoxazoles (3).



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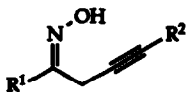

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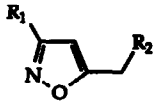


3

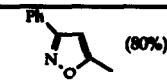
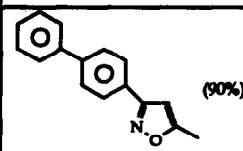
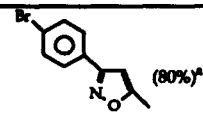
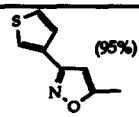
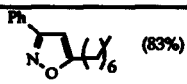
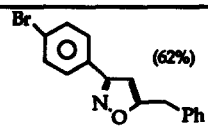
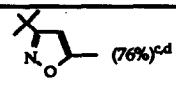
A variety of propargyloximes (2) were prepared efficiently from α-bromoketones following conventional methods[5b,6]. Treatment of (2) with methanolic K_2CO_3 at ambient temperature produced the isoxazole 3 (Equation 1). The conditions for ring closure are quite mild relative to the other reported cyclizations of functionalized propargylamines[3,4].

(1)

2 3

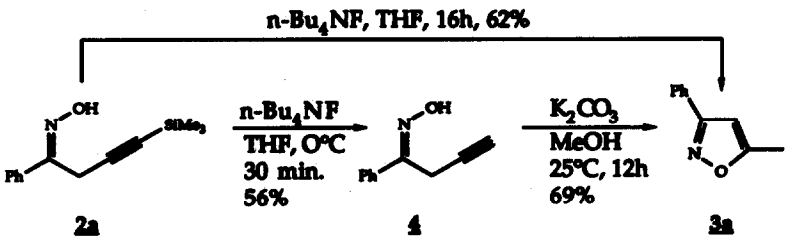
A representative sampling of those isoxazoles synthesized by this method are shown in Table 1.

Table 1: Synthesis of 3,5-Disubstituted Isoxazoles 3 from Propargyl Oximes 2.

Entry	Propargyl Oxime 2	Yield from α-Bromooxime	Isoxazole 3 (Isolated Yield)
a	R^1 = Ph R^2 = $Si(CH_3)_3$	66	 (80%)
b	R^1 = 4,4'-biphenyl R^2 = $Si(CH_3)_3$	49	 (90%)
c	R^1 = 4-bromophenyl R^2 = $Si(CH_3)_3$	60	 (80%)[a]
d	R^1 = 3-thienyl[b] R^2 = $Si(CH_3)_3$	61	 (95%)
e	R^1 = Ph R^2 = C_6H_{13}	44	 (83%)
f	R^1 = 4-bromophenyl R^2 = Ph	68	 (62%)
g	R^1 = t-butyl R^2 = $Si(CH_3)_3$	-	 (76%)[c,d]

a) see ref. 8
b) α-Bromoketone synthesis: see ref. 7
c) Yield from α-bromoketone; oxime not isolated.
d) ref. 9

In entries a-d and g the trimethylsilyl groups present in the starting oximes are lost at some stage of the cyclization sequence. Presumably, the basic methanolic K_2CO_3 desilylates these oximes prior to cyclization. In one case this occurred under slightly different reaction conditions. The terminal propargyloxime (4) was isolated by brief exposure of 2a to n-Bu_4NF (Scheme 2). When 4, in turn, was treated with methanolic K_2CO_3 the isoxazole (3a) was generated as before. Alternatively, prolonged exposure (16h) of 2a to the basic fluoride source also generated the isoxazole (3a) (62%).



Scheme 2

In conclusion, we have demonstrated a novel method of preparing 3,5-disubstituted isoxazoles[10] from β,γ-acetylenic oximes by treatment with mild base.

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8. A representative procedure is as follows: To a solution of (trimethylsilyl)acetylene (1.9 ml., 13 mmol.) in THF (40 ml.) at -78°C was added n-BuLi (2.5 M., 3.3 ml, 8.3 mmol). To this was added 2,4'-dibromoacetophenone oxime (1.01 g., 3.4 mmol) in THF (15 ml). After warming to room temperature for 60 minutes, the mixture was diluted with ether and quenched with NH_4Cl (sat.). The ethereal phase was washed with HCl (1x), brine (1x), and then dried ($MgSO_4$). After filtration and concentration the brown residue was chromatographed on silica gel to give alkyne 2c (0.635 g., 60%) as a colorless solid; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 9H, $-Si(CH_3)_3$), 3.49 (s, 2H, $-CH_2-$), 7.34-7.47 (dd, 4H, ArH), 10.19 (br s, 1H, OH). The alkyne (0.349 g., 1.1 mmol) was reacted with potassium carbonate (1.56 g) in methanol (15 ml) for 12 hrs., then evaporated in vacuo. The residue was retreated with water and ethyl acetate. The organic phase was washed with 5% HCl (2x), brine (1x), then dried ($MgSO_4$), filtered and evaporated to a residue, which was then chromatographed on silica gel to give the isoxazole 3c (0.214 g, 80%) as white plates (m.p. 96-98°C (Et_2O-hexane)); ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3H, CH_3), 6.26 (s, 1H, H-4), 7.55-7.66 (dd, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.34 (CH_3), 99.53 (C-5), 124.03, 128.18, 128.21, 132.04 (Ar C's), 161.60, 170.23 (C-3, C-4); Mass (CI) : 238 $(MH)^+$,

255 $(M+NH_4)^+$; Anal. Calcd. for $C_{10}H_8BrNO$: C 50.45; H 3.39; N 5.88; Br 33.56. Found: C, 50.37; H 3.42; N 5.86; Br 33.29.

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