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Regioselective Syntheses of 3-Aminomethyl-5-substituted Isoxazoles: A Facile and Chemoselective Reduction of Azide to Amine by Sodium Borohydride Using 1,3-Propanedithiol as A Catalyst.

Yazhong Pei* and Barbara O. S. Wickham

Chiron Corporation, 4560 Horton Street, Emeryville, CA 94608

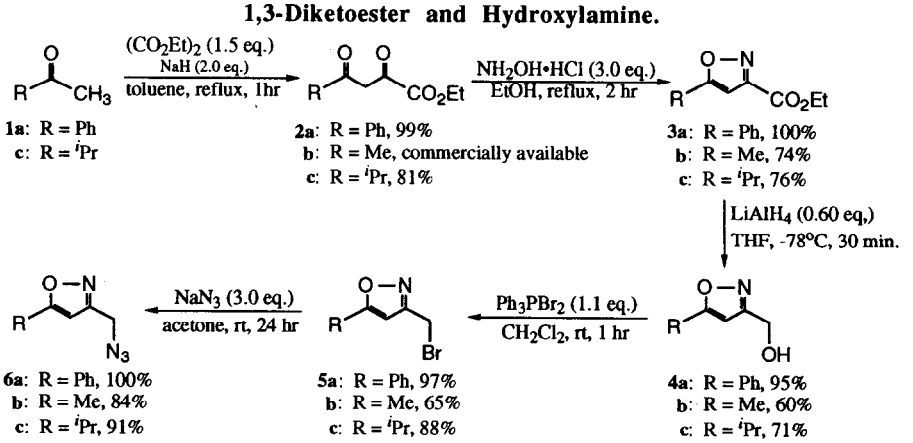
Key words: regioselective synthesis, isoxazoles, catalytic reduction, azide, sodium borohydride, 1,3-propanedithiol.

Abstract: A series of isoxazole azides were reduced selectively to isoxazole amines in quantitative yield by sodium borohydride using 1,3-propanedithiol as a catalyst.

Organic azides can be reduced to amines by a variety of reducing agents.[1] However, the most commonly used methods, such as catalytic hydrogenation and lithium aluminum hydride, are rather unselective. As a result, many chemoselective methods have been developed. Examples include Cr^{II}/H^+,[2] Zn/HCl,[2] Ph_3P/base,[3] H_2S/pyridine,[4] 1,3-propanedithiol/TEA,[5] H_2/Lindlar catalyst,[6] Bu_3SnH/AIBN[7] and $NaBH_4$/phase transfer catalyst.[8] All of these methods are reported to work well in reducing specific azides to amines. In our case, however, the isoxazole moiety of the azides appeared sensitive to many of these reduction conditions. Therefore, a new and efficient method for converting isoxazole azides to the corresponding amines was developed. Herein reported is a facile and chemoselective reduction of isoxazole azides to the corresponding amines by sodium borohydride using 1,3-propanedithiol as a catalyst. This method has the potential for general applicability.

As part of a drug discovery program involving the design and synthesis of novel amines to be used in submonomer solid-phase peptoid synthesis,[9] a short and efficient synthesis of a series of aminomethyl isoxazoles was developed. The synthesis of isoxazole azide **6** is illustrated in Scheme 1. Methyl ketone **1** was condensed with diethyl oxalate in the presence of sodium hydride in refluxing toluene to afford 2,4-diketoester **2**.[10] Diketoester **2** was converted to isoxazole ester **3** upon reaction with hydroxylamine hydrochloride in refluxing ethanol.[11,12] Isoxazole ester **3** was reduced to the corresponding alcohol **4** using lithium aluminum hydride in THF at -78°C. Alcohol **4** was treated with triphenylphosphine dibromide to furnish bromide **5**, which was converted to isoxazole azide **6** by reaction with sodium azide in acetone. In theory, azide **6** can be converted to the corresponding amine **7** by using any number of reduction conditions.

Scheme 1: Synthesis of Isoxazole Azide *via* Condensation of 1,3-Diketoester and Hydroxylamine.



Scheme 2: Catalytic Reduction of Isoxazole Azide to Isoxazole Amine by $NaBH_4$ Using 1,3-Propanedithiol as A Catalyst.

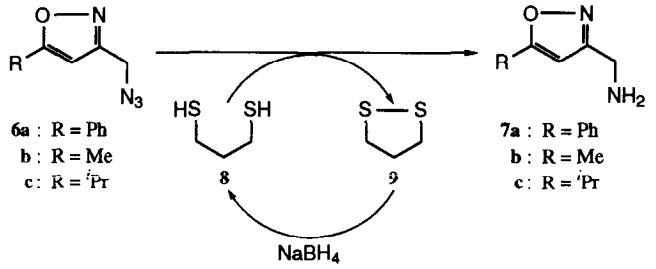


Table 1: Conversion of Isoxazole Azide 6 to Isoxazole Amine 7.

Entry	Azide	Catalyst	Solvent	Reducing Agent	Base	Reaction time(hr)	Yield(%)
1	**6a**	Pd/C	CH_3OH	H_2	-	8	0[a]
2	**6a**	Pd/C(Pb)	CH_3OH	H_2	-	8	0[a]
3	**6a**	Pd/C(Pb)	THF	H_2	-	10	0[a]
4	**6a**	Pd/C(Pb)	EtOAc	H_2	-	10	0[a]
5	**6a**	-	CH_3OH	$HS(CH_2)_3SH$ (2 eq.)	TEA (2 eq.)	18	95[b]
6	**6a**	$HS(CH_2)_3SH$ (0.10 eq.)	CH_3OH	$NaBH_4$ (15 eq.)[c]	TEA (2 eq.)	3	91[b]
7	**6a**	$HS(CH_2)_3SH$ (0.10 eq.)	EtOH	$NaBH_4$ (10 eq.)	TEA (2 eq.)	3	93[b]
8	**6a**	$HS(CH_2)_3SH$ (0.10 eq.)	^iPrOH	$NaBH_4$ (10 eq.)	TEA (2 eq.)	3	97[b]
9	**6a**	$HS(CH_2)_3SH$ (0.01 eq.)	^iPrOH	$NaBH_4$ (1.5 eq.)[d]	TEA (2 eq.)	22	98[b]
10	**6b**	$HS(CH2)3SH$ (0.01 eq.)	^iPrOH	$NaBH4$ (1.5 eq.)	TEA (2 eq.)	24	98[b]
11	**6c**	$HS(CH_2)_3SH$ (0.01 eq.)	^iPrOH	$NaBH_4$ (1.5 eq.)	TEA (2 eq.)	24	70[b]
12	**6a**	-	EtOH	$NaBH_4$ (10 eq.)	TEA (2 eq.)	20	0[e]
13	**6a**	-	CH_3OH	$NaBH_4$ (10 eq.)	-	20	0[e]

[a] All starting material is consumed, however, no desired product is observed. [b] d Isolated yield. [c] 10 eq. $NaBH_4$ was used to start the reaction, and an additional 5 eq. $NaBH_4$ was added after 2 hr to push the reduction to completion. [d] 1.0 eq. $NaBH_4$ was used to start the reaction, and an additional 0.5 eq. $NaBH_4$ was added after 17 hr. [e] No reaction occurred.

The conversion of azide **6** to amine **7** was attempted using various conditions; the results are summarized in Table 1. Catalytic hydrogenation of **6a** did not give the desired isoxazole amine **7a** (Table 1, entry 1), even when mild catalytic hydrogenation conditions were used (entries 2 through 4). This could be due to the cleavage of the N-O bond of the isoxazole moiety under these reaction conditions. It was reported that 1,3-propanedithiol (**8**) reduced organic azides selectively to amines, itself being oxidized to the cyclic disulfide **9**.[5] While this method worked well in our case, converting azide **6a** to amine **7a** in 95% yield, the unpleasant odor of 1,3-propanedithiol (**8**) made this procedure less than desirable, since excess **8** (2-5 eq.) was required for complete reduction.[5] It is known that sodium borohydride does not reduce azides under normal conditions,[8] but does reduce disulfides to thiols. Based on this information, the reduction of azide **6** to amine **7** with sodium borohydride using 1,3-propanedithiol (**8**) as a catalyst (Scheme 2) was investigated. As shown in Table 1, sodium borohydride efficiently reduced isoxazole azide **6a** to isoxazole amine **7a** in the presence of 0.1 equivalent of 1,3-propanedithiol (entries 6 through 8). A solvent effect on this reaction was observed due to differences in the rate of decomposition of sodium borohydride in the alcoholic media. When the reduction is carried out in isopropanol using 1.5 eq. sodium borohydride and 0.01 equivalent of 1,3-propanedithiol (**8**), azides **6a**, **6b**, **6c** were reduced to **7a**, **7b**, **7c**, respectively, in quantitative yields (entries 9, 10, 11). To confirm that 1,3-propanedithiol (**8**) was indeed acting as a catalyst in this reduction, the reaction was carried out with **6a** in the absence of **8** with or without triethylamine (entries 12, 13). As expected, no reduction was observed, and **6a** was recovered in almost quantitative yield.

In the isoxazole ring formation step (Scheme 1), isoxazole ester **3** was obtained exclusively as a single regioisomer in all cases. The regiochemistry of the isoxazole moiety was determined at the final stage by comparison of physical properties with authentic samples prepared from a regiochemically defined pathway.[12,13]

A typical experimental procedure for reducing azide to amine is described below. To a solution of **6a** (6.56 g, 32.7 mmol) in isopropanol (100 ml) at room temperature with vigorous stirring was added triethylamine (9.11 ml, 65.4 mmol), 1,3-propanedithiol (3.27 ml of 0.10 M solution in isopropanol, 0.327 mmol) and sodium borohydride (1.24 g, 32.7 mmol). The mixture was stirred at room temperature and monitored by TLC. After 17 hr, TLC indicated that some starting material remained, so additional sodium borohydride (0.62 g, 16.4 mmol) was added. After 5 more hours, the reaction was complete. Solvent was removed under vacuum, and the residue was dissolved in 10% aqueous citric acid (150 ml) and washed with ether/hexane (1/1, 3x150 ml). The aqueous layer was basified to pH 12 using 6 N aqueous NaOH, saturated with NaCl, and extracted with methylene chloride (4x200 ml). The combined methylene chloride extracts were dried over anhydrous Na_2SO_4, and concentrated to yield isoxazole amine **7a** as a white solid (5.43 g, 98%).[14]

In conclusion, we have demonstrated that sodium borohydride with 1,3-propanedithiol as a catalyst is an efficient alternative method for the reduction of azides to the corresponding amines in the presence of other sensitive functional groups.

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References and Notes.

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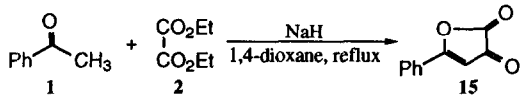
10. The product of this reaction is solvent dependent. When this reaction is carried out in refluxing 1,4-dioxane, lactone **15** is obtained exclusively instead of the desired 2,4-diketoester **2**.



1 2 15

11. When this reaction is carried out in the presence of base (Et_3N or $NaHCO_3$), the desired isoxazole ester **3** is obtained in very low yield (<10%). It appears that *in situ* generated HCl promotes isomerization of the acyclic oxime intermediates, pushing the equilibrium to the most thermodynamically stable product, isoxazole ester **3**.
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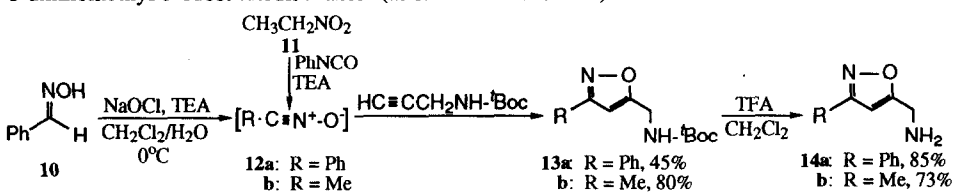
13. The synthesis of regiochemically defined isoxazole amine **14** is illustrated below: nitrile oxides **12a** and **12b** were generated *in situ* from benzaldehyde oxime (**10**) and nitroethane (**11**), respectively. [3+2] Cycloaddition of **12** with ^{t}Boc-protected propargylamine furnished isoxazole **13**. Deprotection of **13** with TFA afforded the authentic sample **14**. Since 5-aminomethyl-2-substitutedisoxazole (**14a** and **14b**) exhibits distinctly different physical properties from **7a** and **7b** respectively,[14] **7** was assigned to be 3-aminomethyl-5-substitutedisoxazole (as shown in Scheme 2).



10 12a: R = Ph, b: R = Me 13a: R = Ph, 45%, b: R = Me, 80% 14a: R = Ph, 85%, b: R = Me, 73%

14. **7a**: mp 70-71 °C; ^{1}H NMR ($CDCl_3$) δ 1.57(bs, 2H), 4.00(s, 2H), 6.53(s, 1H), 7.45(m, 3H), 7.77(m, 2H); IR (cm^{-1}) 3350-2500(b), 1612, 1572, 1493, 1449, 1339, 1261, 1050, 865, 761. **14a**: mp 49-51 °C; ^{1}H NMR ($CDCl_3$) δ 1.57(bs, 2H), 4.02(s, 2H), 6.46(s, 1H), 7.45(m, 3H), 7.77(m, 2H); IR (cm^{-1}) 3350-2500(b), 1597, 1580, 1472, 1444, 1410, 1339, 1168, 1076, 997, 928, 808, 763. **7b**: yellowish liquid; ^{1}H NMR ($CDCl_3$) δ 1.75(bs, 2H), 2.42(s, 3H), 3.89(s, 2H), 5.96(s, 1H); IR (cm^{-1}) 3372, 3303, 3129, 2927, 1606, 1479, 1451, 1373, 1257, 1170, 1007, 889, 804, 735. **14b**: yellowish liquid; ^{1}H NMR ($CDCl_3$) δ 1.56(bs, 2H), 2.28(s, 3H), 3.94(s, 2H), 5.97(s, 1H); IR (cm^{-1}) 3600-2800(b), 2998, 2912, 1653, 1436, 1419, 1313, 1072, 954, 703. ^{1}H NMR of mixtures of **7a** and **14a**, **7b** and **14b** showed two sets of peaks which confirmed that **7a** and **7b** are different from **14a** and **14b**, respectively.

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