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Unexpected 1,3-Oxazolidine Formation in the Attempted Oxidation of *N*-Aryl-*N*-Methyl Substituted β-Amino Alcohols using Pyridinium Dichromate

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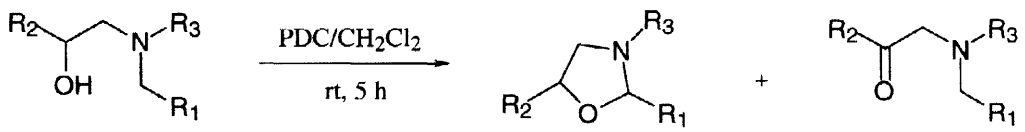
Abstract: 1,3-Oxazolidines were obtained from the reaction of *N*-methyl substituted β-amino alcohols with pyridinium dichromate in dichloromethane. A single electron transfer mechanism, SET, is proposed to account for the formation of the 1,3-oxazolidines.

The oxidation of primary alcohols to aldehydes and secondary alcohols to ketones with pyridinium dichromate (PDC) is a well established procedure in synthetic organic chemistry, owing mainly to the mild reaction conditions employed.[1,2] However, while attempting to oxidize the hydroxy group of 3-(4-methoxyphenyl)-1-[(*N*-methyl-*N*-phenyl)amino]-2-propanol **1a** to its corresponding ketone **3a**, the 1,3-oxazolidine **2a** was obtained as the unexpected major product[3]; the desired ketone **3a** being obtained in only a poor yield of 4% (Scheme 1).



1a-k **2a-k** **3a-k**

Scheme 1

A number of methods exist for formation of 1,3-oxazolidines, including preparation from β-amino alcohols and carbonyl compounds.[4,5] Typically this condensation is carried out under relatively harsh conditions in refluxing benzene or toluene, the reaction being driven to completion by an azeotropic distillation. A few stereoselective and stereospecific routes to 1,3-oxazolidines have also been presented. A method of particular interest is the stereospecific formation of 1,3-oxazolidines from (-)-ephedrine and acetylenic or allenic sulphones.[6] Harding *et al.* have investigated the stereoselective mercuric ion-initiated cyclization of acylaminomethyl ether derivatives of acyclic allylic alcohols to form 4,5-disubstituted 1,3-oxazolidines.[7,8] This intramolecular amidomercuration lends itself to the convenient synthesis of non-proteinogenic β-amino acids.[9] To our knowledge, however, the 1,3-oxazolidine formation using the oxidative conditions described above is unprecedented.

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To investigate the general applicability of this new transformation, a variety of *N*-aryl-*N*-methyl-β-amino alcohols were reacted with pyridinium dichromate, the results are summarized in table 1. The β-amino alcohols **1a-k** were prepared by treatment of the corresponding epoxides[10] with a diethylaluminium amide in dichloromethane at room temperature.[11] After mild acidic hydrolysis (excess saturated NH_4Cl at rt, 2 h), the β-amino alcohols were oxidized with pyridinium dichromate in dichloromethane at room temperature.[12] These oxidation reactions afforded *N*-aryl-1,3-oxazolidines **2a-e** and **2g-h** in moderate to excellent yields.[13]

Table 1. Oxidation of *N*-Aryl-*N*-Methyl β-Amino Alcohols with PDC in CH_2Cl_2.

Compound	R_1	R_2	R_3	Yield (%)[a]	
				1,3-Oxazolidine	Ketone
a	H	4-$MeOC_6H_4CH_2$	Ph	93	4
b	H	$PhCH_2$	4-MeC_6H_4	51	26
c	H	$PhCH_2$	Ph	68	17
d	H	$PhCH_2$	4-$MeOC_6H_4$	89	3
e	H	$PhCH_2$	4-ClC_6H_4	72	4
f	Me	$PhCH_2$	Ph	-	13
g	H	Me	Ph	46	-
h	H	$CH_2CHCH_2CH_2$	Ph	46	-
i	H	$CH_2CHCH_2CH_2$	$PhCH_2$	-	13
j	H	$PhCH_2$	Me	-	-
k	H	$PhCH_2$	Et	-	-

[a]The reaction time was 5 hours.

In a typical procedure, a mixture of β-amino alcohol **1a-k** (0.20 mmol) and pyridinium dichromate (0.30 mmol) in CH_2Cl_2 (15 ml) was stirred at room temperature for 5 h. The mixture was then filtered through a pad of $MgSO_4$ and evaporated *in vacuo*. The crude product residue was purified by silica gel chromatography with hexane-acetone (4:3) as the eluent. The 1,3-oxazolidines, **2a-e** and **2g-h**, are only slightly polar compounds and can be easily identified and isolated as the highest R_f value compounds.

The best results were obtained from the reactions of the β-amino alcohols **1a** and **1d** while the yields of cyclization were moderate when the *para* substituent of the *N*-aryl moiety of the β-amino alcohol was methyl **1b** or chlorine **1e**. A benzylic $\mathbf{R_2}$ group α to the alcohol functionality is not a requirement for oxidative ring closure, as demonstrated by entries **g** and **h**. This finding suggests that a wide range of *N*-aryl-*N*-methyl β-amino alcohols could be employed as precursors for oxazolidine formation. Examples **i**, **j** and **k**, on the other hand, illustrate that an *N*-aryl $\mathbf{R_3}$ group is needed for successful cyclization. The *N*-alkyl-*N*-methyl-β-amino alcohols **1j** and **1k** gave no detectable products whereas the *N*-benzyl-*N*-methyl compound led to a poor yield of the corresponding ketone (13%) and a small amount of benzaldehyde (14%). Interestingly, the reaction of *N*-ethyl-*N*-phenyl-β-amino alcohol **1f**, with PDC also gave no detectable amount of the cyclized 2-methyl-1,3-

oxazolidine product and only a poor yield of the ketone. Steric interactions may be in part responsible for such results. Of further note is that in the case of the β-amino alcohol **1e**, the formation of 1,3-oxazolidine was accompanied by some dealkylation of the aromatic tertiary amine, supported by isolation of the byproduct, *N*-(4-chlorophenyl)-β-amino alcohol, in a yield of 11%.

A potential mechanism that could account for the formation of 1,3-oxazolidines from the reaction of these *N*-aryl-*N*-methyl-β-amino alcohols with pyridinium dichromate invokes a single electron transfer process (SET).[14] Chromium oxide has been shown to initiate SET processes[15] and the 1,3-oxazolidine species formed and the oxidative dealkylation[16] observed in the reaction of **1e** could both be linked *via* an SET mechanism. Detection of the benzaldehyde byproduct following the oxidation of **1i** also suggests an initial formation of an aminium cation radical, *via* SET, with the subsequent loss of a hydrogen atom. The resultant iminium species is then hydrolyzed to the aldehyde. Such an SET process has been linked to the oxidative dealkylation of other tertiary amines using metal oxidants such as permanganate,[17] $CoCl_2$, CuCl,[18] and iron(III) or manganese(III) complexes[19]. Further investigations are clearly warrented to dissect this reaction pathway and the products observed.

In conclusion, a novel method for the preparation of *N*-aryl-1,3-oxazolidines from *N*-aryl-*N*-methyl-β-amino alcohols has been discovered. While the reaction mechanism has yet to be elucidated, the overall simplicity may prove to be of general interest as *N*-aryl-1,3-oxazolidines can be readily converted into *N*-aryl-β-amino alcohols by hydrolytic methods.[20] Finally, chiral cyclic 1,3-oxazolidines, which can be derived from enantiomerically pure β-amino alcohols, have been widely used as chiral auxiliaries.[21]

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References and Notes

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