2-OXAZOLINES FROM AMIDES VIA IMIDATES†

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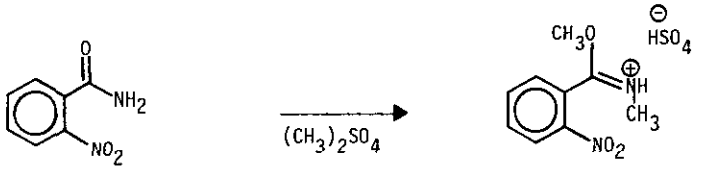
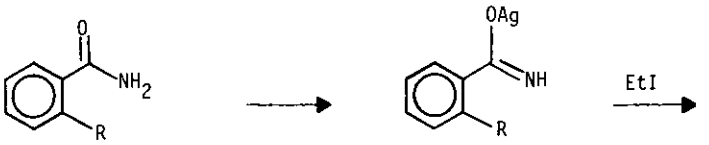
Chiral oxazolines useful in asymmetric synthesis of o-substituted phthalides and benzoic acids are readily prepared from the benzamides via their imino ethers.

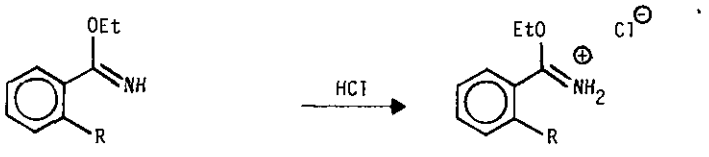
The development of new methods of preparing chiral 2-oxazolines from functional groups other than those previously reported in the literature, i.e., imino ether hydrochlorides,[1] has been a continuing effort in our laboratories. These imino ether hydrochlorides are typically prepared from nitriles under rather vigorous conditions, ethanol and dry hydrogen chloride.[2] Our need for ortho substituted phenyl chiral oxazolines 11 and the incompatibility of these conditions with hindered nitriles,[3] i.e., ortho substituted benzonitriles, points out the necessity of developing a new method.

Two reports[4,5] have appeared in the literature where ortho substituted benzamides have been alkylated to form imidates. These include the alkylation of o-nitrobenzamide with dimethyl sulfate, and the alkylation of silver salts of amides, followed by reaction with HCl to form imidates (equations 1 and 2). A report[6] that amides also reacted with triethyloxonium



(1)



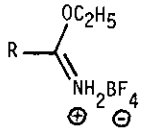


(2)

R = Cl or CH_3

†Dedicated to Professor T. Kametani on the occasion of his retirement from Tohoku University.

tetrafluoroborate[7] in methylene chloride forming imidate 1 (which is structurally similar to imidate 2) indicated the possibility of using this species as an oxazoline precursor. Herein we report the use of imidate 1 for the synthesis of chiral oxazolines.



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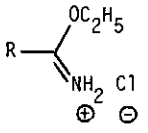
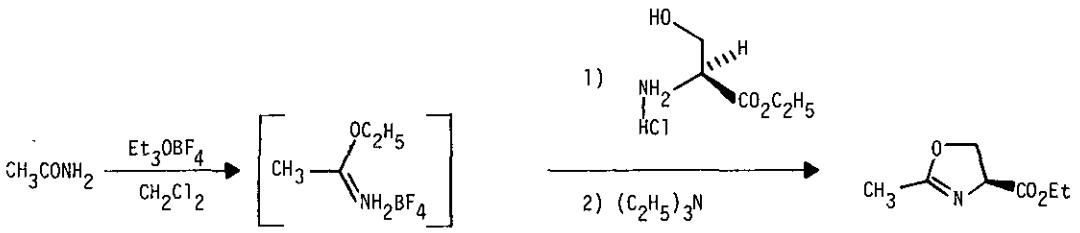


2

The simple amide, acetamide, was chosen for the preliminary studies. Reaction of a methylene chloride solution of this amide with triethyloxonium tetrafluoroborate (RT, 16-20 hours), gave a slightly cloudy solution which presumably contained the imidate 3 in situ. Addition of ethyl-L-serinate hydrochloride[8] to this mixture followed by treatment with triethylamine (RT, 16 hours), resulted in the formation of the corresponding oxazoline, 4a.

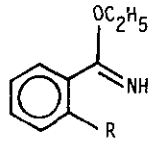


3 4a

Similarly, reaction of a 1,2-dichloroethane solution of o-bromobenzamide with triethyloxonium tetrafluoroborate in 1,2-dichloroethane (RT, 16-20 hours), followed by the addition of L-(+)-threo-1-phenyl-2-amino-3-methoxy-1-propanol[1] 10 (refluxing $ClCH_2CH_2Cl$, higher temperatures are needed for aromatic oxazoline formation, 18 hours), provided the aromatic oxazoline 11b.

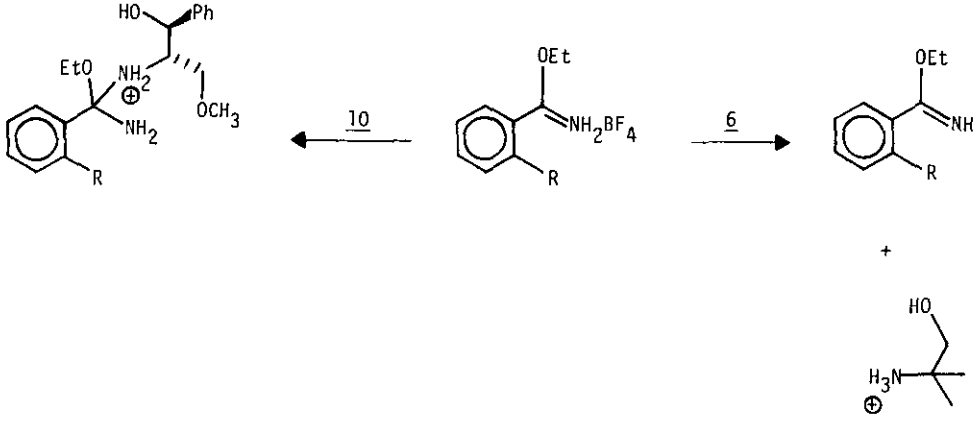
Several examples, showing the versatility of this method for preparing chiral oxazolines from alkyl and aryl amides, are given in Table 1.

For the case of ortho substituted benzamides, when oxazoline formation was incomplete, the only by-product was the imino ether 12. The ratio of oxazoline to imino ether depends on the amino alcohol and on the imidate used in the reaction (Table 2). Since there are no reaction intermediates isolated, it is assumed that once the amino alcohol adds to the imidate, the reaction proceeds to completion. The difference in oxazoline to imino ether ratios with several amino alcohols and imidates must then be determined by the initial addition step.



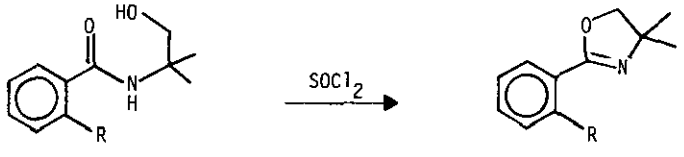
12

The first step[9,10] in oxazoline formation is the addition of the free amine to the imidate. Addition is slow for the hindered amino alcohol 6. Deprotonation of the imidate can occur preventing oxazoline formation. Addition is fast for the less hindered amino alcohol 10 providing excellent yields of the oxazolines.



Reactivity also depends on the acidity of the imidate. Jencks[11] has shown that the more acidic m-nitro benzimidate (pK_a 5.30) is less reactive with amines than benzimidate (pK_a 6.37). A similar trend is seen with the ortho substituted benzimidates (Table 2). The more acidic o-bromo and o-methyl benzimidates are much less reactive than the o-methoxy benzimidate.

This method is poor for the synthesis of oxazolines 7a and 7b, however, these oxazolines are conveniently prepared by cyclization of amide 13.[12] Nevertheless, this method gives excellent yields of the chiral oxazolines 11b, 11c, and 11d. Currently this is the only known method for preparing these oxazolines.



R = Br or CH_3 13

7a, R = Br

7b, R = CH_3

Table 1 - Oxazolines from Amides via Imidates

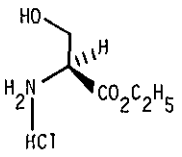
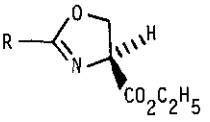
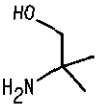
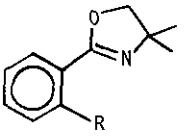
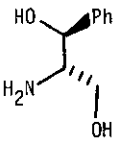
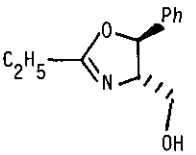
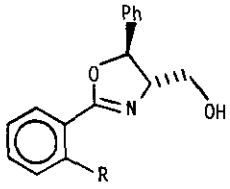
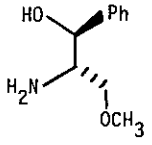
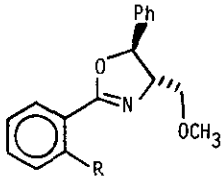
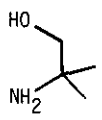
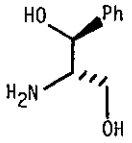
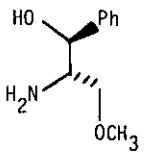
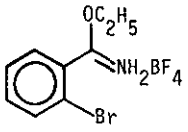
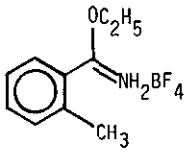
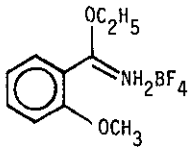
Amide	Amino Alcohol	Product (Yield)	$[\alpha]_D$
1) acetamide	 5	 4a, R = CH_3 (54%)	+170°[a]
2) benzamide	5	4b, R = C_6H_5 (91%)	+123°[b]
3) o-bromobenzamide	 6	 7a, R = Br (trace)	--
4) *o-methylbenzamide*	6	7b, R = CH_3 (trace)	--
5) o-methoxybenzamide	6	7c, R = OCH_3 (80%)	--
6) propionamide	 8	 (54%)	-134.3°[c]

Table 1 - Continued

7) o-bromobenzamide	8	 9a, R = Br (50%)	--
8) o-methylbenzamide	8	9b, R = CH_3 (60%)	+36.8°
9) benzamide	 10	 11a, R = H (81%)	+65.2°[d]
10) o-bromobenzamide	10	11b, R = Br (82%)	+19.3°
11) o-methylbenzamide	10	11c, R = CH_3 (85%)	+57.7°
12) o-methoxybenzamide	10	11d, R = OCH_3 (82%)	+58.1°

a) Lit. $[\alpha]_D$ = +181.5°, ref. 8; b) Lit. $[\alpha]_D$ = +134.5°, ref. 13; c) Lit. $[\alpha]_D$ = -135.1°, ref. 1; d) Lit. $[\alpha]_D$ = +54.1°, ref. 14.

Table 2[a] - Oxazoline/Imino Ether Ratio

Amino Alcohol / Imidate	 6	 8	 10
	5/95 (trace)	60/40 (50%)[b]	100/0 (82%)[b]
	10/90 (trace)	70/30 (60%)[b]	100/0 (85%)[b]
	100/0 (80%)[b]	--	100/0 (82%)[b]

a) % oxazoline/% imino ether determined by H^1-nmr; b) Yield of isolated oxazoline.

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