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STEREOCHEMISTRY OF THE Ph_3P-CCl_4 MEDIATED CYCLIZATION OF CARBOXYLIC ACIDS AND 1,2-AMINO ALCOHOLS (VORBRUGGEN METHOD)

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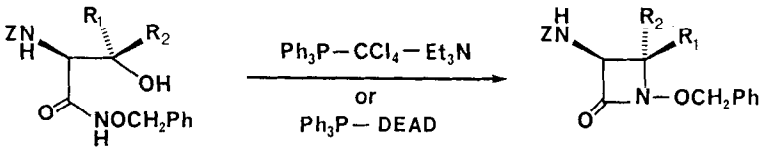
Summary: In contrast to a previous report, β-hydroxy amides formed via the Ph_3P-CCl_4 condensation of acids and amino alcohols, cyclize to oxazolines with complete inversion of the carbinol center.

The condensation of carboxyl groups and other nucleophiles with alcohols using Ph_3P-DEAD has become an important technique in synthesis and is now known as the Mitsonobu reaction.[1] Recently, this has been extended by Miller[2] to the synthesis of β-lactams 2 by intramolecular cyclization of β-hydroxy hydroxamic acids 1 with Ph_3P-DEAD. The process proceeded with clean inversion at the carbinol center. Furthermore, the use of Ph_3P-CCl_4-Et_3N, previously utilized to transform alcohols to halides[3] and amino alcohols to

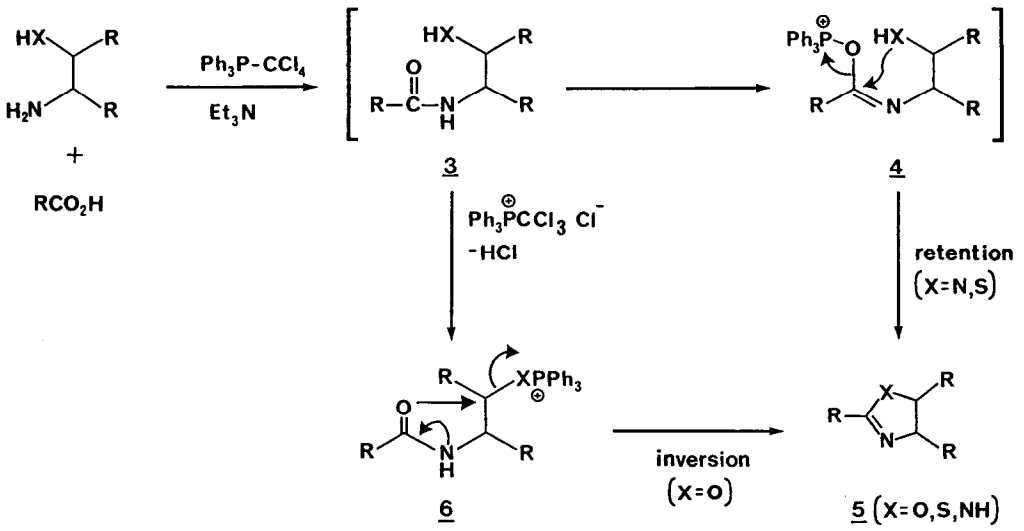


2

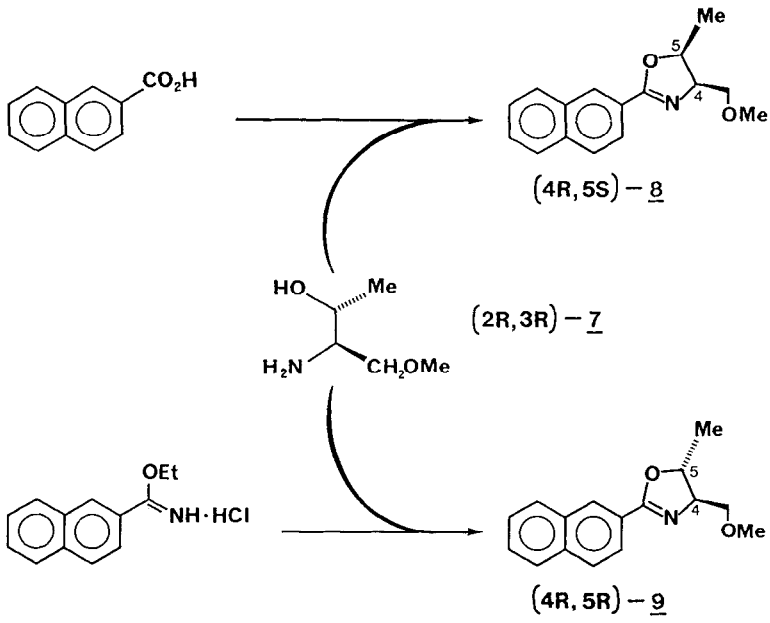
1a, $R_1 = R_2 = H$
1b, $R_1 = Me$, $R_2 = H$
1c, $R_1 = H$, $R_2 = Me$

aziridines,[4] also converted 1 to 2 with complete inversion. Another recent report by Vorbruggen[5] described a facile synthesis of oxazines, oxazolines, thiazolines, and imidazolines by employing Ph_3P-CCl_4-Et_3N to condense carboxylic acids with amino alcohols, mercaptoamines, and diamines, in a single step (Scheme 1). Although we have found this to be an excellent approach to these heterocycles, we were surprised to find the process differs from the mechanism claimed by Vorbruggen, but consistent with the claims of Miller.[2] We examined the oxazoline route described by Vorbruggen using 2-naphthoic acid and (2R, 3R)-3-amino-4-methoxy-2-butanol 7 obtained from threonine[6] and hoped to obtain the naphthyl oxazoline 9 needed for our studies on nucleophilic addition to chiral naphthalenes.[7] Instead, when the Vorbruggen conditions were applied, the only product

Scheme 1

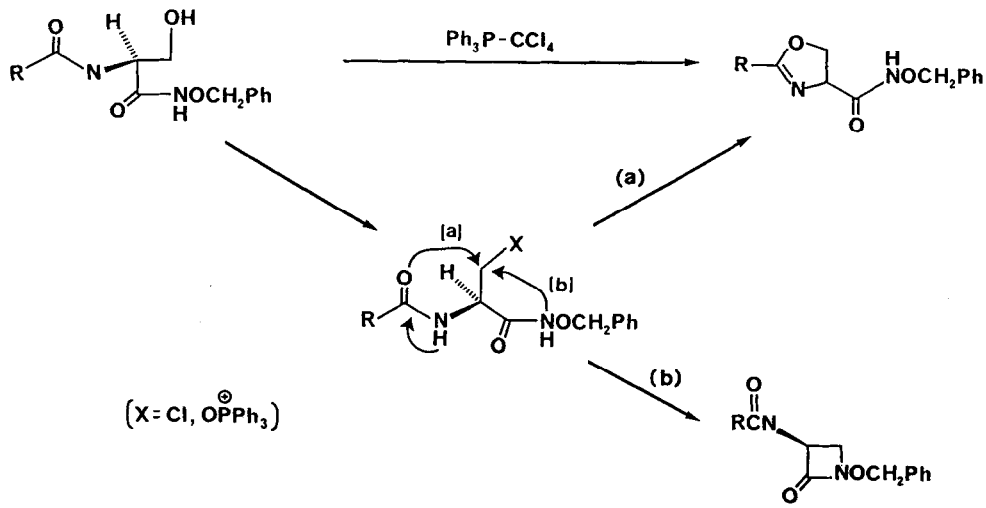


obtained, in 75% yield, was the oxazoline 8 which had clearly undergone inversion at C-5. The cis alignment for C-4, C-5 in 8 was confirmed by an NOE determination. Irradiation of the C-5 methyl in 8 exhibited only a strong NOE for the vicinal proton at C-5 and no effect upon the distant proton at C-4. On the other hand, the trans-oxazoline 9 was prepared using the naphthylimidate, known to proceed with retention on 7 and the NOE showed the expected C-4 signal enhancement. Thus, we had confirmed the fact that the sequence described by Vorbruggen (Scheme I), indeed, proceeds with inversion when amino alcohols are employed using the Ph_3P-CCl_4-Et_3N reagent. Apparently the Vorbruggen study was misled by the use of mercaptoamines 4 (X = S) or diamines 4 (X = NH) which produced heterocycles 5 containing sulfur and nitrogen. Since they did not use amino alcohols possessing a secondary alcohol,[8] only primary alcohols, it could not be utilized as a probe for stereochemical results. Therefore, the intermediate hydroxy amide 3 (X = O) reacts primarily with $Ph_3P^{\oplus}$-$CCl_4^{\ominus}$ at the hydroxyl group and displacement occurs by the amide carbonyl, as shown in 6, with inversion. The affinity of oxygen for phosphorous over that by nitrogen or sulfur is presumably the major reason that ring closure to 5 takes place in



two different manners. As stated earlier, the work by Miller[2] (1 ⟶ 2) is consistent with the inversion of secondary alcohols under these conditions. Ironically, Miller also reported an oxazoline formation in his β-lactam work when 1 (Z = $PhCH_2CO$) was employed, but R_1, R_2 were hydrogens (1a) and thus he was not in a position to detect the inversion

Scheme 2



during oxazoline ring closure (Scheme 2). Nevertheless, he suggested that since the only products isolated were β-lactam and oxazoline as shown in Scheme 2, that the oxyphosphonium salt is more likely to be the leaving group.

In summary, the Vorbruggen method to generate heterocycles is one of considerable utility, in view of the single step, one-pot reaction, but proceeds with high stereochemical control (inversion) when amino alcohols are employed and with retention when diamines or mercaptoamines are used.

References and Notes

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4. R. Appel and R. Kleinstuck, Chem. Ber. 107, 5 (1974); T. Okada, K. Schimura, and R. Sudo, Bull. Chem. Soc. Japan 43, 1185 (1970).
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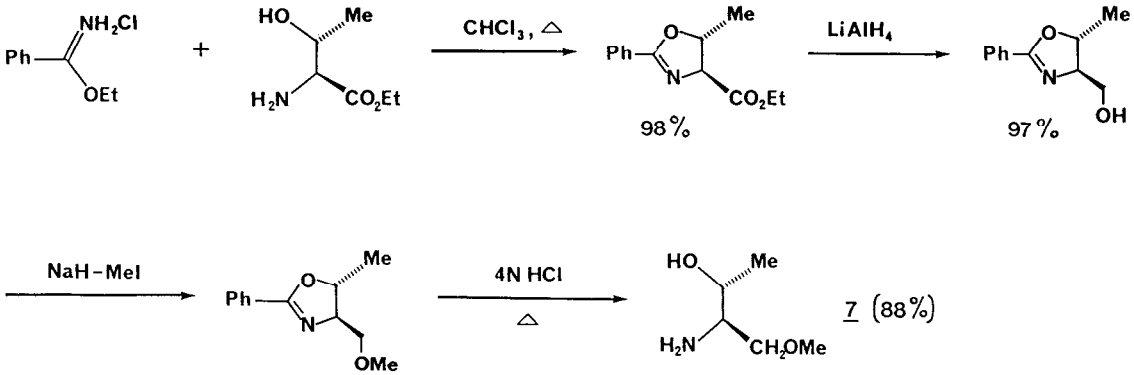
6. Threonine was transformed via the oxazoline to the methoxyamino carbinol 7 according to the following sequence. The overall yield of 7 was 80%, mp 54-55°, $[\alpha]_D$ + 6.37° (c 5.7, $CHCl_3$).



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8. Vorbruggen (ref 5) attempted an oxazoline synthesis with a phenyl carbinol but reported no yield of product.

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