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HETEROCYCLES IN SYNTHESIS. DIPEPTIDES VIA UNMASKING OF 5-ACYL- AND 5-ACYLOXYAMINOOXAZOLES

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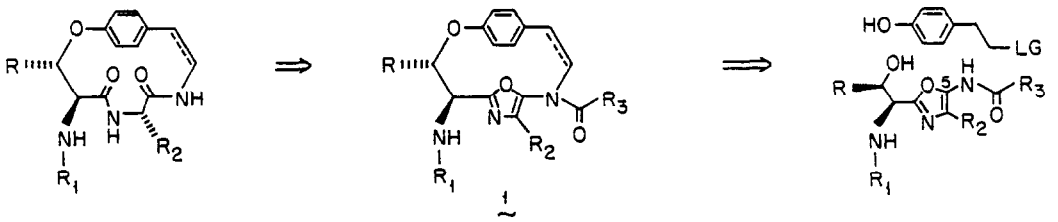
SUMMARY: *Heteroaromatic oxazole rings, when substituted in the appropriate fashion, may be unmasked to afford dipeptides in excellent yields.*

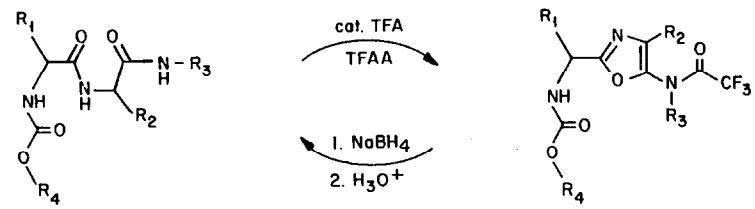
Central to our efforts aimed at developing new strategies en route to the Cyclopeptide Alkaloids,[1] a fairly large class of potential specific ion sequestering agents,[2] is the ultimate unmasking of derivatized 5-aminooxazoles to their corresponding dipeptides. We have recently detailed a number of routes to both 5-acyl- and 5-acyloxyaminooxazoles,



and very briefly alluded to their eventual ring opening to diamides/dipeptides.[1] In this Letter, we now report that this concept is quite general, and may be used to selectively elaborate dipeptides disguised in the form of oxazoles. Two independent modes of unraveling are documented, including one fascinating and unexpected case employing optically pure material, which leads to chiral induction at an originally racemic center.

About a decade ago, Fleury, et al,[3] showed that secondary and tertiary aryl-substituted-5-aminooxazoles are relatively unstable and readily undergo hydrolysis to diamides. Based on this early work, we prepared tertiary trifluoroacetamides 4[4] and 5[4] from dipeptides 2 and 3 in very high isolated yields[1] using catalytic TFA, and 2.5 equiv

TFAA in CH_2Cl_2. It was anticipated that reductive removal of each trifluoroacetamide[5] followed by hydrolysis would reform the corresponding dipeptide. In the event, treatment of



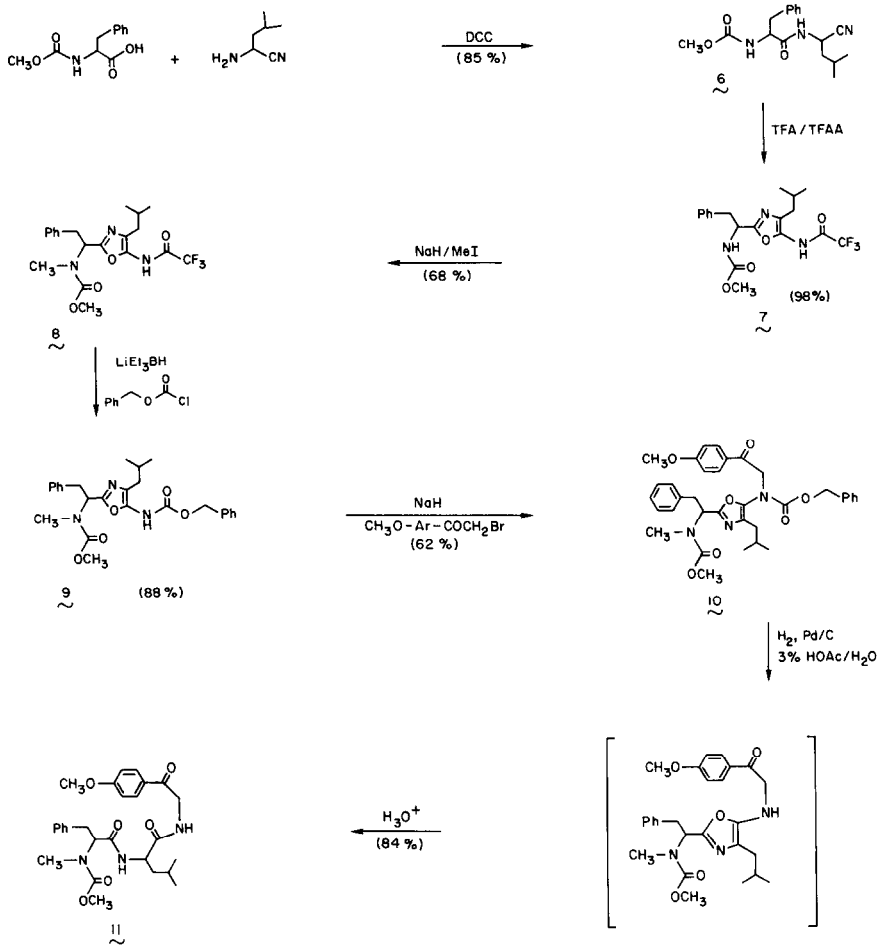
2	R_1 = H, R_2 = R_3 = R_4 = CH_2Ph	4 (92 %)
3	R_1 = CH_2Ph, R_2 = i-Bu, R_3 = C_3H_5, R_4 = CH_3	5 (90 %)

4 and 5 with $NaBH_4$ in EtOH at -78°C → rt with subsequent addition of each mixture to dilute acetic acid (0°, 15 min) afforded the respective dipeptides in 89 and 93% yields after purification. Thus, the correspondence between 5-acylaminooxazoles and dipeptides has been demonstrated.

As noted previously,[1,6] trifluoroacetamides of type 4 and 5 do not readily undergo alkylation at the amide nitrogen. This observation does have some virtue in that it allows the selective N-alkylation of the urethane (vide infra). Moreover, to extend the value of the TFA/TFAA-based cyclization, an exchange process employing, initially SuperHydride,[7] followed by reaction with an acyl halide or chloroformate has been developed,[1] thereby resulting in 5-aminooxazole derivatives of our choosing. In light of the availability and well known utility of Cbz-Cl,[8] replacement of a trifluoroacetamido group with a carbobenzyloxy moiety was envisioned to permit future oxazole unmasking in a single pot via catalytic hydrogenation in the presence of aqueous acid. Thus, as illustrated in Scheme 1, cyclization of urethano-nitrile 6 affords oxazole 7.[4] Regiospecific N-alkylation leads to 8[4] which upon anion formation ($LiEt_3BH$), imide generation (Cbz-Cl), and workup (H_2O, $-COCF_3$) gives 9.[4] Urethane alkylation with the α-bromoketone of p-methoxyacetophenone results in 10,[4] a species formally one carbon-oxygen bond away from the desired cyclophane 1. The key transformation to 11[4] was effected in 84% yield by simply treating 10, dissolved in EtOH containing a few drops of 3% aqueous HOAc, with a catalytic amount of 10% Pd/C under a balloon of hydrogen.

Finally, we mention an interesting experimental finding along these lines which may have significant future implications. Cyclization of Cbz-ℓ-Leu-dℓ-Phe-N-benzyl amide, prepared in the traditional way,[8] with TFA/TFAA affords 13[4] in 98% yield. Exposure of 13 to $NaBH_4$ supported on neutral alumina[9] in CH_2Cl_2 at 0°C → rt (so as to avoid the highly basic medium of $NaBH_4$/EtOH) removes the CF_3CO- group.[10] Inverse addition of the solution obtained upon filtration to dilute aqueous HOAc, while indeed returning the starting dipeptide (86%), led not to the original 1:1 mix of diastereomers, but rather to a 6.5:1 ratio of ℓℓ to ℓd

SCHEME I



12 (1:1, ℓℓ:ℓd) → 13 (ℓ only, 98 %)

13 (ℓ) → 12 (6.5:1, ℓℓ:ℓd; 86 %)

dipeptides.[11] Thus, ca. 70% chiral induction accompanied ring opening!

In conclusion, highly substituted 5-aminooxazoles[12] have been shown to be functionally equivalent to dipeptides. A single ring closure step affords heterocycles which are eventually unmasked under the influence of either mild hydride or H_2, followed by dilute aqueous acid. Prior to dipeptide generation, these heterocycles may be further elaborated in the form of N-alkylation, C-alkylation,[1] or acyl exchange processes. A similar unraveling sequence applied to a stereodefined educt apparently results in the induction of chirality at an initially racemic center. The scope of this new methodology, both as a general tool for inducing optical activity in natural as well as synthetic amino acids and within the context of natural products synthesis, will be reported in due course.

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10. The intermediate secondary amine is clearly discernable by TLC.
11. Determined by HPLC analysis on a Waters M-6000A analytical system using a radially compressed 5μ silica gel cartridge, with 0-2% isopropanol in $CHCl_3$ at 3 mL/min over 15 min. The precursors (diastereomers 11) gave a 1:1 ratio under similar conditions.
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