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ON THE FACILE DEHYDROHALOGENATION OF AMINO ACID DERIVED CHLOROMETHYL KETONES.

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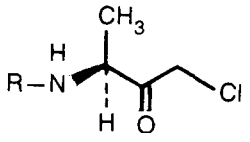
SUMMARY: Amino acid derived chloromethyl ketones are shown to undergo a general dehydrohalogenation reaction under mild, basic, non-nucleophilic conditions to afford α-β-unsaturated ketones.

Halomethyl ketone derivatives of amino acids comprise an extremely well-known class of chemical substances which are frequently utilized as active site probes in the elucidation of structural and mechanistic details of proteolytic enzyme reactions.[1] Except for their interaction with enzymic functionalities, the chemistry of amino acid derived halomethyl ketones has not been well defined. In the course of another research problem, we observed that Cbz-L-alanine derived chloromethyl ketone 1, upon exposure to Et_3N/benzene/26°C, was converted to α-β-unsaturated ketone 2. This observation seemed related to an earlier report of Shaw and Ruscica[2] which mentioned without elaboration the reaction of Tos-PheCH_2Cl[3] (5) with N-benzoyl-His-OCH_3 (EtOH, 50°C, 5 h) to give unsaturated ketone 6. These authors also noted that Cbz-PheCH_2Cl (7) failed to undergo a similar transformation. In contrast, we found that 7, when treated with Et_3N/CH_2Cl_2/ 26°C, underwent facile dehydrohalogenation leading to 8 [76%, mp 64-65°C; IR (KBr) 1720, 1660, 1628 cm^{-1}; ^{13}C NMR (CD_3CN) δ 26.0, 67.6, olefinic carbons obscured by aromatics, 154.0, 196.0; ^1H NMR ($CDCl_3$) δ 2.4 (s, 3H), 5.1 (s, 2H), 6.8 (br s, 1H, ex.), 7.1 (s, 1H)].

This paper summarises efforts aimed at defining the scope and mechanism of this interesting reaction which in fact we find to be quite general. Initial studies focused on the role of the nitrogen bearing moiety. In addition to a sulfonamide or urethane substituent, 2° amides were shown to be compatible with dehydrohalogenation. Hence, N-benzoyl-PheCH_2Cl (9) and N-benzoyl-AlaCH_2Cl (3) underwent smooth transformation to ketones 10 (58%, mp 100-101°C) and 4 [90%, IR ($CHCl_3$) 1712, 1664 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 23.4, 109.9, 138.1, 165.4, 194.6; ^1H NMR ($CDCl_3$) δ 2.4 (s, 3H), 5.9 (d, 1H), 7.1



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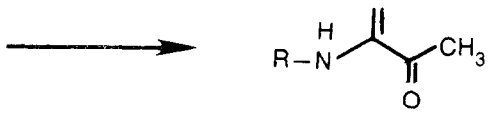
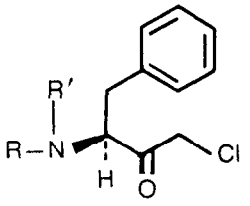
3, R = $PhCO-$



2, R = $PhCH_2OCO-$

4, R = $PhCO-$

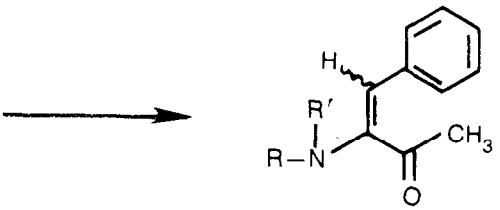


5, R = $4-CH_3PhSO_2-$, R′ = H

7, R = $PhCH_2OCO-$, R′ = H

9, R = $PhCO-$, R′ = H

11, R = $PhCH_2OCO-$, R′ = CH_3

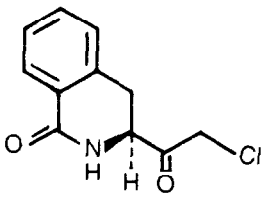


6, R = $4-CH_3PhSO_2-$, R′ = H

8, R = $PhCH_2OCO-$, R′ = H

10, R = $PhCO-$, R′ = H

12, R = $PhCH_2OCO-$, R′ = CH_3



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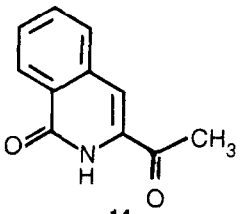

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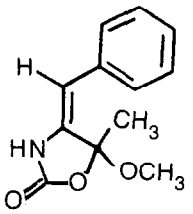

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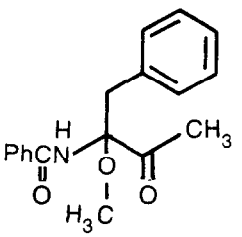

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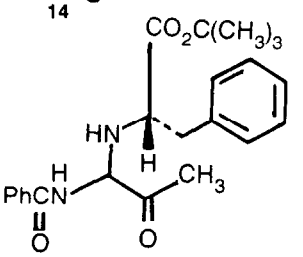

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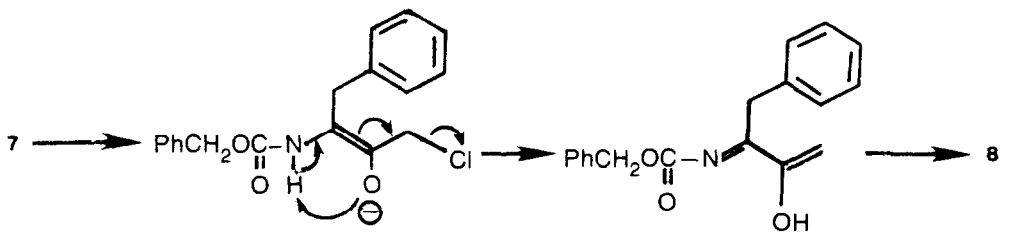

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16

(s, 1H); MS m/e 190 (M+H).[4]

Alkylation of the amino acid nitrogen resulted in an adverse effect on the elimination. Thus, N-CBz-N-methyl-PheCH_2Cl (11) was inert to standard reaction conditions (Et_3N/CH_2Cl_2/26°C or Et_3N/CH_3OH/reflux), however, heating under reflux in chloroform produced fair yields ($\cong$25%) of α-β-unsaturated ketone 12 as a mixture of isomers.[5]

In considering a viable mechanistic pathway for the general case (*i.e.*, 9→10), the fact that N-tosyl derivative 5 is converted to 6 discounts a transitory participation by side chain acyl oxygen. This conclusion is supported by related results obtained with conformationally restricted analog 13, which undergoes very facile conversion to 14 [40%, IR (KBr) 1660, 1600 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.2, 112.1, 127.9, 128.2, 128.6, 129.7, 132.9, 135.7, 161.1, 190.7], wherein geometrical constraints prohibit such anchimeric assistance. Powers has suggested the intermediacy of an N-chloro moiety[1] which presumably could arise *via* an intramolecular C→N halogen shift and then suffer dehydrohalogenation followed by tautomerism to give 6. The fact that N-alkyl substrates undergo the reaction even in modest yield strongly argues against this process, as does our observation of the nearly quantitative transformation of N-Cbz-Phe$CH_2OSO_2CH_3$[6] to 8, since C→N transfer of a methanesulfonyloxy group is extremely unlikely. At this point, a mechanism involving a sequence such as 7→15→16→8 seems most probable.[7] Efforts aimed at trapping either intermediate 15 or 16, by performing the reaction of 7 in methanol, instead afforded as the major product substance 17 [68%, 148-149°C; IR (KBr) 1780, 1690, 1665 cm^{-1}; ^{13}C NMR (CD_3CN) δ 26.1, 51.0, 101.9; ^1H NMR ($CDCl_3$) δ 1.8 (s, 3H), 3.35 (s, 3H), 5.65 (s, 1H), 8.5 (br s, ex.); MS m/e 219 (M^+), structure confirmed by X-ray crystallography]. Interestingly, treatment of 8 with Et_3N/CH_3OH did not afford 17 (no reaction) suggesting that it is not a precursor in genesis of the latter. On the other hand, exposure of 9 to CH_3OH/Et_3N afforded methoxy amide 18 as the major product [55%, 156-157°C, IR (KBr) 1730, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.34 (d, 2H, J=13 Hz), 3.35 (s, 3H), 4.09 (d, 1H, J=13HZ)], presumably by addition of methanol to an acylimine similar to 16. In another experiment, introduction of phenylalanine *t*-butyl ester trapped the acylimine arising from N-benzoyl-GlyCH_2Cl to give 19 as a mixture of diastereomers [IR ($CHCl_3$) 1725, 1661 cm^{-1}; ^{13}C NMR ($CHCl_3$) δ 25.9, 26.7, 40.2, 59.3, 60.8, 68.9, 69.5, 173.2, 174.1, 203.4, 204.3; MS m/e 397 (M+H)].

In conclusion, we have demonstrated that amino acid derived chloromethyl ketones undergo a quite general dehydrohalogenation under mild, basic, non-nucleophilic conditions to afford α-β-unsaturated ketones. In view of the fact that the mechanistic details of the present process remain to be fully elucidated, and that in addition to the products, at least one putative

reaction intermediate (acylimine) is an extremely reactive species, potentially susceptible to attack by enzymic functionality, caution may be warranted in the interpretation of enzyme modification studies with this class of inhibitors. Enzymic bases of sufficient strength to initiate this dehydrohalogenation process have been observed,[8] and in fact we found that even imidazole (CH_2Cl_2/26°C) is sufficient to induce a quantitative conversion of 7 to 8.

ACKNOWLEDGEMENT: We thank Dr. Scott Biller for useful discussions, The Squibb Institute Analytical Department for assistance in obtaining spectral and microanalytical data, and Dr. J. Z. Gougoutas and Ms. M. Malley for X-ray crystallographic analyses.

REFERENCES:

1. J. C. Powers in "Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins", Vol. 4, pp 65-178, B. Weinstein, Ed., Marcel Dekker, New York, 1977, and references therein.
2. E. Shaw and J. Ruscica, *Arch. Biochem. Biophys.*, 145, 484 (1971).
3. This nomenclature for amino acid derived halomethyl ketones is used in accordance with reference 1, p. 68.
4. Substance 4 was too unstable to permit satisfactory combustion analysis.
5. This is the only example in which we detected *syn-anti* isomerism.
6. D. Larsen and E. Shaw, *J. Med. Chem.*, 19, 1284 (1976).
7. See also, P. A. Wender, J. M. Erhardt, and L. J. Letendre, *J. Am. Chem. Soc.*, 103, 2114 (1981), and references therein.
8. Kaiser has reported the carboxypeptidase A catalyzed enolization of 2-benzyl-3-*p*-methoxybenzoyl propionate [T. Sugimoto and E. T. Kaiser, *J. Am. Chem. Soc.*, 101, 3946 (1979)] and a related enzyme catalyzed α,β-elimination reaction [N. T. Nashed and E. T. Kaiser, *J. Am. Chem. Soc.*, 103, 3611 (1981)].

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