

ONE CARBON UNIT TRANSFER TO ENAMINES THROUGH OXAZOLIDINES AND
TETRAHYDRO-2H-1,3-OXAZINE

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Abstract - Oxazolidines and tetrahydro-2H-1,3-oxazine undergo acid catalysed transfer of C₂ carbon unit inbetween two nucleophilic carbons of stabilised enamines.

Like THF model 1-methyl-3-tosyl/acetyl imidazolidine derivatives¹, oxazolidines and thiazolidines irrespective of the presence or absence of electron donating group at nitrogen, demonstrate carbonyl group oxidation level carbon transfer character to binucleophiles, i.e. C, N; N, N etc.² The N⁵,N¹⁰-methylenetetrahydrofolate induced reductive methylation³ of 2'-deoxyuridylate to 2'-deoxythymidylate involves the initial transfer of CH₂(C₂) of imidazolidine ring, at formaldehyde level to enamine β-carbon (C₅)⁴ of uracil moiety. Consequently, for understanding the mechanistic features, the investigation of such carbon transfer reactions on enamines are significant.⁵ Here we report that oxazolidines and tetrahydro-2H-1,3-oxazine perform acid catalysed transfer of C₂ carbon unit inbetween nucleophilic carbons of two molecules of relatively stable enamines and form methylene bis-enamine adducts which may undergo further transformations.

Ethyl β-aminocrotonate, a relatively stable enamine⁶, with 2-phenyl-3,4,4-trimethyl-oxazolidine (1a) or 2-phenyl-4,4-dimethyloxazolidine (1b) in acetonitrile at room temperature in the presence of a catalytic amount of acetic acid furnish diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (2a). Likewise, 3-phenyloxazolidine (1c) and ethyl β-aminocrotonate yield diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (2b) (Table). Ethyl β-anilino crotonate also reacts with (1a), (1b) and (1c) to furnish corresponding dihydropyridine derivatives, 2c and 2d, respectively (Table).

Evidently, alkylidene imines, (6, R=H, Ph; R⁵=COOEt; R³=H, Ph; R⁶=Me), generated through β-elimination of (5), which are tautomers of the initial adducts (4) formed from protonated oxazolidines and enamines, react with a second molecule of enamine to form adducts which through cycloelimination finally yield 2a - 2d. In case of a similar reaction of oxazolidine with an enamine lacking H at nitrogen corresponding 7 is formed through cycloaddition reaction of the initial adduct (4)⁷ which cannot exist as tautomer (5). Thus the absence or presence of H at nitrogen of enamine directs the course of its reaction with an oxazolidine (Scheme).

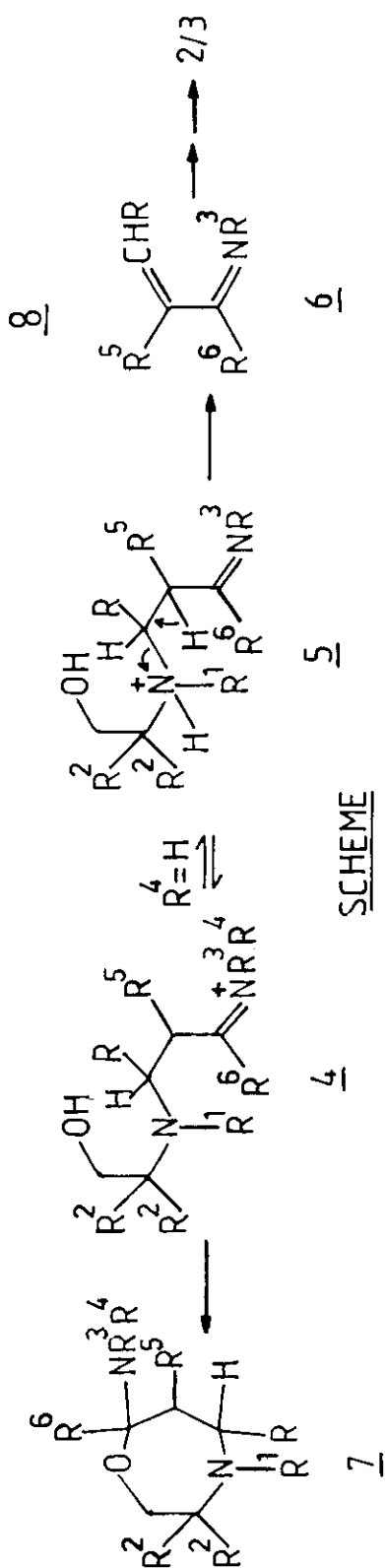
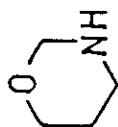
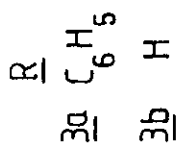
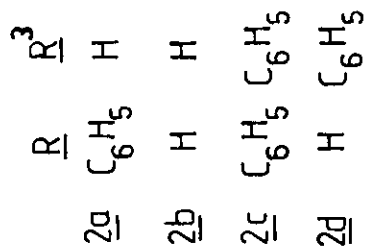
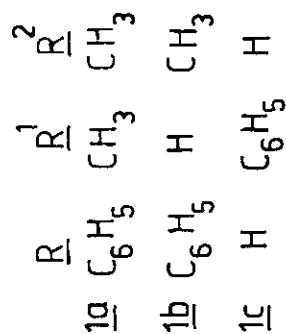
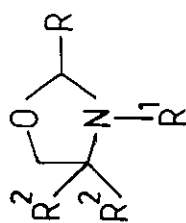
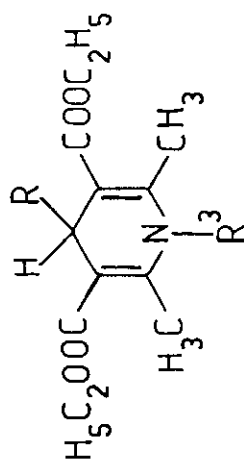
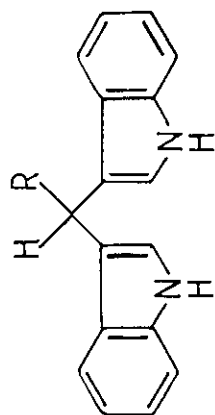
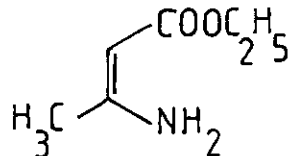
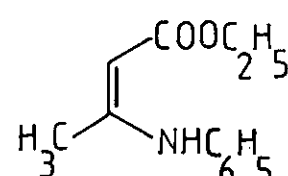
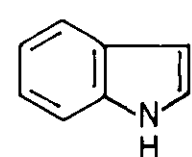


Table: Reactions of Enamines with oxazolidines and tetrahydro-2H-1,3-oxazine

Reagent	Enamine	Product ^a	m.p.(°C)	Time(h)	Yield(%)
<u>1a</u>		<u>2a</u>	156	6.0 ^b	73
<u>1b</u>		<u>2a</u>	-do-	4.5 ^b	70
<u>1c</u>		<u>2b</u>	182.5	3.0 ^b	80
<u>8</u>		<u>2b</u>	-do-	0.1 ^b	90
<u>1a</u>		<u>2c</u>	155	6.0 ^b	40
<u>1b</u>		<u>2c</u>	-do-	8.0 ^b	35
<u>1c</u>		<u>2d</u>	99	2.5 ^b	70
<u>8</u>		<u>2d</u>	-do-	0.7 ^b	65
<u>1a</u>		<u>3a</u>	127	8.0 ^c	53
<u>1b</u>		<u>3a</u>	-do-	18.0 ^d	55
<u>1c</u>		<u>3b</u>	164	12.0 ^b	55
<u>8</u>		<u>3b</u>	-do-	3.0 ^d	70

a - For all the compounds satisfactory spectral data and/or comparison with authentic samples have been obtained. b - In $\text{CH}_3\text{CN}/\text{CH}_3\text{COOH}$ at room temperature. c - In refluxing $\text{CH}_3\text{CN}/\text{CH}_3\text{COOH}$. d - In refluxing $\text{CH}_3\text{CN}/\text{CH}_3\text{COOH}$.

Indole undergoes electrophilic reactions at position 3 and has an enamine character. It reacts with 2-phenyl-3,4-trimethyloxazolidine (1a)/2-phenyl-4,4-dimethyloxazolidine (1b) in refluxing acetonitrile under acidic conditions to furnish 3,3'-phenylmethylene-bis(1H-indole) (3a). In a similar reaction, 3-phenyloxazolidine (1c) and indole furnish 3,3'-methylene-bis(1H-indole) (3b) (Table). These products are analogs of streptindole, a genotoxic metabolite.⁸

The carbonyl character of saturated C_2 unit of tetrahydro-2H-1,3-oxazines and functionalization of C_2 -alkyl chain of their precursor 5,6-dihydro-2H-1,3-oxazines has been demonstrated.⁹ By the same argument as was advanced for oxazolidines², tetrahydro-2H-1,3-oxazines could also act as carbon transfer agents. Thus we have found that tetrahydro-2H-1,3-oxazine (8) reacts advantageously (Table) with ethyl β -aminocrotonate, ethyl β -anilincrotonate and indole in acetonitrile in the presence of acetic acid to furnish 2b, 2d and 3b respectively. Further synthetic utility of tetrahydro-2H-1,3-oxazines is being investigated.

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