

Synthesis of Pyrazolidines (5-membered heterocyclic rings) through 1, 3- dipolar cycloadditions of azomethine imines.

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Abstract: Dipolar cycloadditions of azomethine imines, formed in situ from aldehydes and hydrazines with electron deficient dipolarophiles produced pyrazolidines. Monosubstituted dipolarophiles afford principally 4-substituted pyrazolidines.

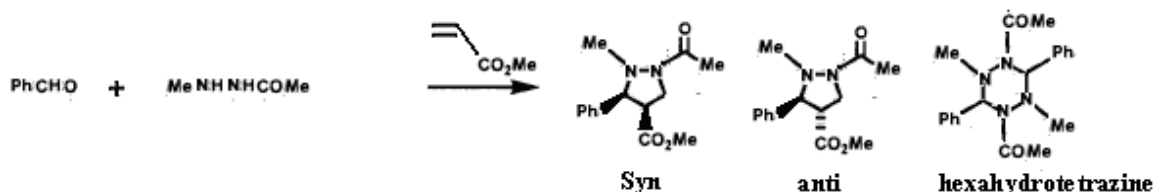
Keywords: dipolarophiles, pyrazolidines

I. Introduction

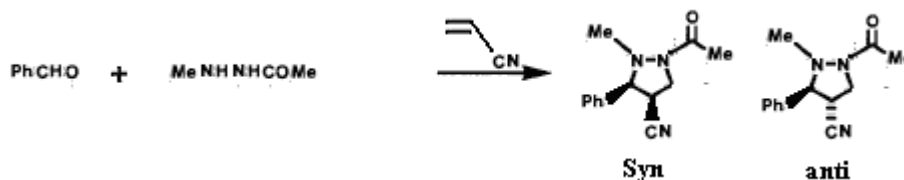
As a part of our research effort for the preparation of peptidomimetics containing 5-membered heterocycles, we have developed a method to synthesize the pyrazolidines. The incorporation of cyclic moiety into peptide backbone can restrict the conformational freedom of peptide and these peptidomimetics can possess enhanced biological activity or increased selectivity towards specific receptor sites. There is an ongoing search for peptide mimetics that incorporate both replacement of important amide bonds and restriction of conformational freedom relative to the native peptide. Such pseudopeptides have potential as agonists or antagonists at peptide, receptor or as inhibitors of peptidase enzymes. One focus of this research is on molecules that enforce reverse turn on a predominantly peptide chain as part of a programme for the incorporation of heterocycles into peptidomimetics. The pyrazolidine ring is accessible via 1,3-dipolar cycloaddition reaction of an azomethine imine with an appropriately substituted alkene that has a potential to generate new chiral centres. It has some control over regio and stereo chemistry of the product.

There are different methods [1]-[5] for the synthesis of substituted pyrazoles. One of them is involving cycloaddition reaction of benzaldehyde, N-acetyl-N-methyl hydrazine and methyl propionate using toluene as a solvent [6]. The chromatographic separation yields both syn and anti 4-methoxy carbonyl pyrazolidines diastereomers. The reaction was carried out under Dean-Stark water removal technique. When the reaction was attempted without water removal or with one mole equivalent of water the syn and anti cycloadducts are formed as minor products whereas hexahydrotriazine was obtained as major product. The presence of water has inhibited the dipole formation for the cycloaddition reaction. The regiochemistry of the products was elucidated by 2D NMR spectroscopy, NOE experiments and X-ray crystallography. Formation of hexahydrotriazine is probably due to dimerization of azomethine imines. Extramolar equivalent of aldehyde results in a slight increase in the yields of syn and anti tetrahydropyrazolidines. Another synthetic method reports the cycloaddition of azomethine imine with acrylonitrile to yield trace amount of syn and anti 4-cyano tetrahydropyrazoles. With symmetrical 1, 2 disubstituted dipolarophile, dimethyl fumarate, a complex mixture of syn and anti isomer was obtained [7]. Cycloaddition reaction of aliphatic aldehyde, N-acetyl-N-methyl hydrazine and vinyl acetate forms tetrahydropyrazole derivatives in moderate yield. With N-acetyl-N-benzyl hydrazine only 4% of tetrahydropyrazole derivative was obtained. (Scheme 1 and 2)

Scheme 1



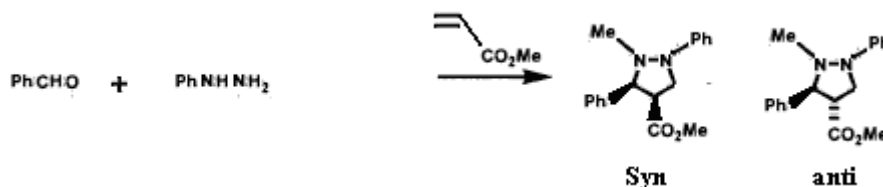
Scheme 2



II. Present work

In the present method, we would like to report the 1,3-dipolar cycloaddition reaction of aromatic aldehydes, phenyl hydrazine and vinyl acetate in moderate to high yield. The reaction was carried out with Dean-Stark apparatus using xylene as a solvent. The products obtained were of better yield and quality. These products were characterized by IR, NMR and Mass spectra. Aromatic ring with electron acceptor group reacts readily and forms product in excellent yield. The electron acceptor group facilitates the nucleophilic addition on carbonyl carbon. With electron donor group on aromatic ring, the reaction is slow and moderate yield of cycloadducts are obtained. After the completion of reaction the solvent was removed by distillation and the crude products obtained were fine crystals with better purity.

Scheme 3



III. Experimental section

General procedure – Benzaldehyde (2.12 g), phenyl hydrazine (2.14 g) and vinyl acetate (0.172 g) were placed in a round bottom flask fitted with a Dean-Stark apparatus using xylene as a solvent. After 48 hours of reflux, the solvent was removed by distillation and the crude product was purified by column chromatography to give syn diastereo isomer. The trans diastereo isomer was also isolated containing traces of impurities. The products are characterized by IR, NMR and Mass spectral data. The results are summarized in a tabular form.

Sr. No.	Aldehyde	Solvent	Reaction time (hrs)	Yield (%)	M.P. (°C)
1	Benzaldehyde	Benzene	72	50	160
2	Benzaldehyde	Xylene	48	60	160
3	Cinnamaldehyde	Xylene	12	85	173
4	Anisaldehyde	Xylene	80	45	118
5	m-Nitrobenzaldehyde	Xylene	10	86	192

Spectral data for tetrahydropyrazole derivative obtained cinnamaldehyde. PMR 200MHz; CDCl₃. 1.2 (br s 1H), 2.05 (br s 2H), 3.35 (s, 4H), 5.25 (d, J= 7Hz, 1H), 6.5 (d, J=13 Hz, 1H), 6.9 (dd, J= 13 and 3Hz, 1H), 7.05 -7.24 (m, 3H, Ar-H), 7.3 – 7.45 (m, 2H)
 IR (KBr/cm⁻¹) 1728, 1640, 1600, 1500, 3300.
 Mass – m/z 196, 168, 92, 77, 50

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