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INTRAMOLECULAR [4+2] CYCLOADDITION OF α,ß-UNSATURATED HYDRAZONES AS A ROUTE TO ANNELATED PYRIDINES

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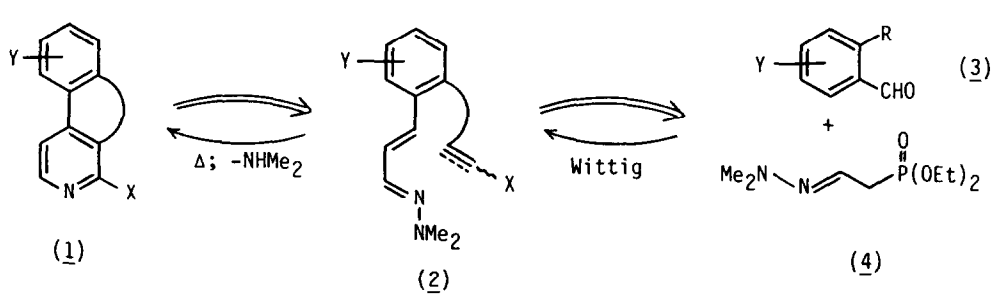
Summary: The first examples of the intramolecular Diels-Alder reaction of α,ß-unsaturated hydrazones are described. A novel phosphonate (4) has been utilized in the preparation of substrates (2).

In conjunction with our interest in the design and synthesis of novel calcium channel antagonists, we required an efficient route to annelated pyridine ring systems (1). The unique substitution pattern present in these structures and the opportunity to investigate new chemistry led us to consider the intramolecular [4+2] cycloaddition reaction of α,ß-unsaturated hydrazones (2). To date the reaction of substituted vinyl hydrazones with appropriate dienophiles has received relatively little attention[1] as compared to other azadiene systems,[2] while the intramolecular version of this reaction is unknown. We describe here our initial studies in this area and present a general strategy for the elaboration of aldehydes (3) to α,ß-unsaturated hydrazones (2) using a novel phosphonate (4).



(1) (2) (4)

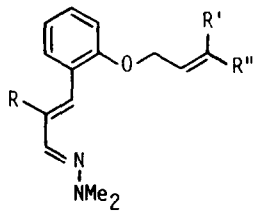
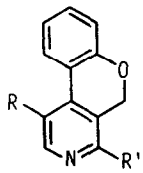
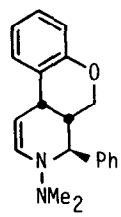
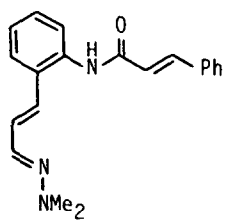
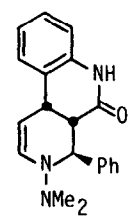
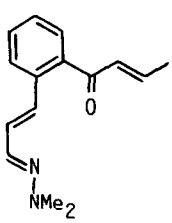
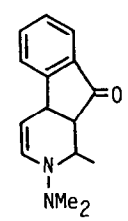
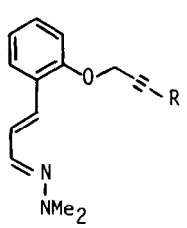
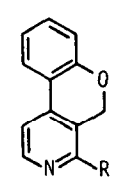
Initial synthesis of the requisite vinyl hydrazone substrates (Table) relied on a 3-step homologation ($Ph_3PCHCOOMe$ → DIBAL → PCC oxidation) of a series of 2-substituted benzaldehydes (3)[3a] to cinnamaldehydes and subsequent condensation with H_2NNMe_2. We found that this 4-step sequence could be reduced to a single step via the direct Wadsworth-Emmons condensation of these aldehydes with the lithium anion derived from phosphonate (4).[4] Thus, deprotonation of (4) (1.1 equiv.) with n-BuLi (1.1 equiv.) at -78 °C and stirring for 15 min followed by the addition of an aldehyde (1.0 equiv.) and warming (-78 → 25 °C; 2 h) gave good yields (50-80%) of the vinyl hydrazones (Table). A variety of aryl and alkyl aldehydes are accommodated as substrates in this reaction and the E vs Z ratios which result from the condensation are high (>10:1).

Intramolecular [4+2] cycloaddition was effected upon heating solutions (0.2 M) of the α,ß-unsaturated hydrazones in either m-xylene or mesitylene at reflux (138-162 °C; 18-48 h; Table). Pyridines (1) were generally obtained directly from the reaction following removal of the solvent and flash chromatography.[3b] In some instances, 1-dimethylaminotetrahydropyridine adducts were identified as the major products in the cycloaddition reaction (entries d, e, f).[5] For entries d and e, the tetrahydropyridines were isolated and the cis-ring junction in these adducts was established by ^1H NMR (NOE). This stereochemical assignment is consistent with a concerted pericyclic reaction proceeding through a syn transition state.[2d,6]

Cinnamyl hydrazones possessing an unactivated allyl ether (entries b and c) were found to be poor Diels-Alder substrates. In these examples, allyl phenols arising from the competing [3,3] sigmatropic rearrangement were identified as the major products of the reaction.

Noteworthy were the cycloadditions of substrates containing the propargyl dienophiles (entries g and h). These substrates underwent smooth intramolecular cyclization and concomitant thermal elimination of dimethylamine affording pyridines in good yield. These types of substrates appear to be ideal for constructing annelated pyridines and are being used in our laboratory to prepare molecules of interest.[7]

Table. Intramolecular [4+2] Cycloadditions of α,ß-Unsaturated Hydrazones (2)

Entry	Substrate	Time (h)/Temp (°C)	Adduct	Yield (%)[a]
				
a	R=H; R'=R"=Cl	48/138	R=H; R'=Cl	34
b	R=R'=R"=H	120/138	R=R'=H	0[b]
c	R=Me; R'=R"=H	18/162	R=Me; R'=H	12[b]
d	R=R'=H; R"=Ph	18/138		80[c]
e		3/114		32[d]
f		48/162		35[e]
				
g	R=H	18/138	R=H	58
h	R=Ph	18/138	R=Ph	74

[a] Isolated yields. [b] Major product derived from Claisen rearrangement. [c] 5% pyridine isolated. [d] Reaction carried out in refluxing toluene. [e] Mixture of isomers obtained.

REFERENCES AND NOTES

1) a) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. Tetrahedron Lett. 1982, 23, 3261. b) Tamura, Y.; Tsugoshi, T.; Nakajima, Y.; Kita, Y. Synthesis 1984, 930. c) Potts, K.T.; Bhattacharjee, D.; Walsh, E.B. J. Chem. Soc. Chem. Commun. 1984, 114. d) Potts, K.T.; Walsh, E.B.; Bhattacharjee, D. J. Org. Chem. 1987, 52, 2285. e) Waldner, A. Eur. Patent 221 023, 1987; Chem. Abstr. 1987, 107, 134210. f) Astles, D.P.; Flood, A. Ger. Patent 3 707 530, 1987; Chem. Abstr. 1988, 108, 37663. g) Waldner, A. Helv. Chim. Acta 1988, 71, 486 and 493.

2) a) Hetero Diels-Alder Methodology in Organic Synthesis; Boger, D.L.; Weinreb, S.M., Ed.; Academic Press: New York, 1987. b) Boger, D.L. Tetrahedron 1983, 39, 2869. c) Kametani, T.; Hibino, S. In Advances in Heterocyclic Chemistry; Katritzky, A.R., Ed.; Academic Press, Inc.: London, 1987; Vol 42, pp 245-333. d) Ciganek, E. In Organic Reactions; Dauben, W.G., Ed.; John Wiley & Sons, Inc.: New York, 1984; Vol. 32, Chapter 1.

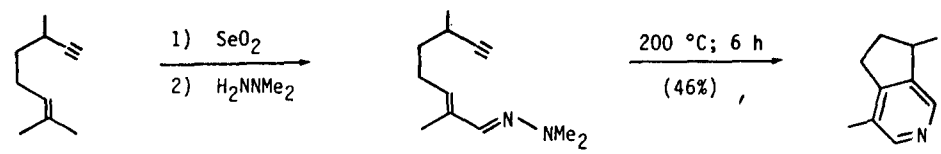
3) a) Preparation of these compounds will be reported elsewhere. b) All new compounds exhibited physical and spectroscopic properties consistent with their structure. For adduct entry d: mp 150-152 °C; ^{1}H NMR δ ($CDCl_3$) 7.34-6.70 (m, 9H, aromatic), 6.39 (dd, 1H, J=2.5, 7.8 Hz), 5.23 (m, 1H), 3.99 (d, 1H, J=10.5 Hz), 3.81 (t, 1H, J=10.5 Hz), 3.66-3.61 (m, 2H), 2.40 (s, 6H, $NNMe_2$), 2.40 (m, 1H); mass spectrum, m/e 306 (M+), 189, 146, 117. For adduct entry h: mp 162-164 °C; ^{1}H NMR δ ($CDCl_3$) 8.68 (d, 1H, J=5.3 Hz, CH=N), 7.81-6.99 (m, 10H, aromatic), 5.20 (m, 2H, OCH_2); mass spectrum, m/e 259 (M+), 231.

4) For the preparation of (4): A solution of diethylformylmethylphosphonate (54 g, 330 mmol; Organic Synthesis; Brossi, A., Ed.; John Wiley and Sons: New York, 1973; Vol. 53, pp 44-48) in CH_2Cl_2 (600 mL) containing anhydrous $MgSO_4$ (110 g) was cooled to 0 °C and freshly distilled H_2NNMe_2 (75 mL, 1.0 mol) added over a 5-10 min period. The reaction was stirred for 2 h, filtered and CH_2Cl_2 removed in vacuo to provide (4) (65 g, 100%, anti isomer only) which was used without further purification. For (4): bp_{10} 122-124 °C; ^{1}H NMR δ ($CDCl_3$) 6.49 (m, 1H, CH=N), 4.12 (m, 4H, OCH_2CH_3), 2.83 (m, 2H, PCH_2), 2.79 (s, 6H, NMe_2), 1.32 (t, 6H, OCH_2CH_3).

5) Dehydrogenation of 1-dimethylaminotetrahydropyridine adducts to pyridines has been reported. See ref 1e-g. We have oxidized the adduct in entry d to the corresponding pyridine by treatment with 10% Pd/C in xylene at 138 °C.

6) Craig, D. Chem. Soc. Rev. 1987, 16, 187.

7) We have also completed a short synthesis of the monoterpene alkaloid (±) actinidine (5) using this methodology. Thus, oxidation of (6) (Snider, B.B.; Killinger, T.A. J. Org. Chem. 1978, 43, 2161) with SeO_2 and then condensation with H_2NNMe_2 gave (7) which underwent smooth intramolecular cycloaddition to (5). This material exhibited physical and spectroscopic properties identical to those reported previously (Davies, L.B.; Greenberg, S.G.; Sammes, P.G. J. Chem. Soc., Perkin Trans. 1 1981, 1909).



(6) (7) (5)

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