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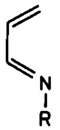
1-AZA-1,3-DIENES. DIELS-ALDER REACTIONS WITH α,β-UNSATURATED HYDRAZONES.

Béatrice Serckx-Poncin, Anne-Marie Hesbain-Frisque and Léon Ghosez*

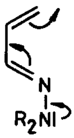
Laboratoire de Chimie Organique de Synthèse,
Université Catholique de Louvain, Place L. Pasteur, 1
B - 1348 LOUVAIN-LA-NEUVE, BELGIUM

Summary : The α,β unsaturated hydrazone 3 reacts regioselectively with a wide range of dienophiles to give the corresponding [4+2] adducts. Reductive cleavage of the N-N bond in the adducts gives tetrahydropyridines.

Dienes incorporating heteroatoms into the conjugated system have not yet received the attention they call for on the basis of their potential for the synthesis of heterocyclic compounds. We have recently revealed[1] the high enophilic reactivity of 2-aza-1,3-dienes bearing ether or amine groups at position 1 or 3. In contrast there are only a few isolated cases[2] of limited synthetic interest in which 1-aza-1,3-dienes 1 were shown to participate in Diels-Alder reactions. This natural reluctance of 1 to undergo [4+2] cycloadditions can however, be readily overcome by entropic assistance as shown by the useful intramolecular Diels-Alder reactions of N-acyl-1-aza-1,3-dienes[3].



1 R = Alkyl, Aryl, OR



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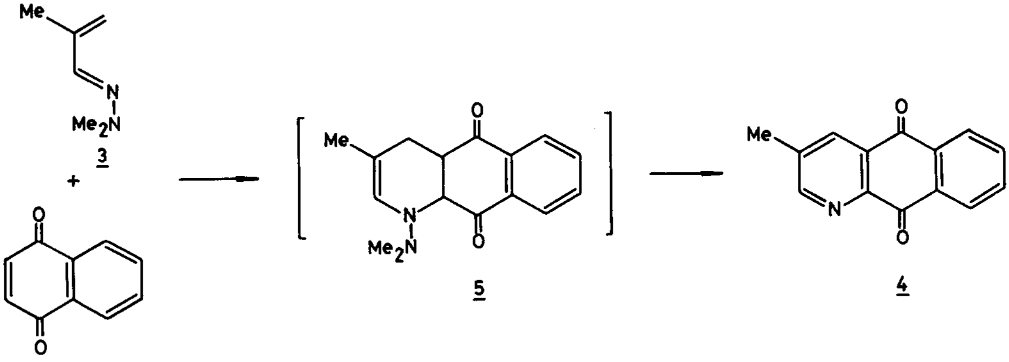
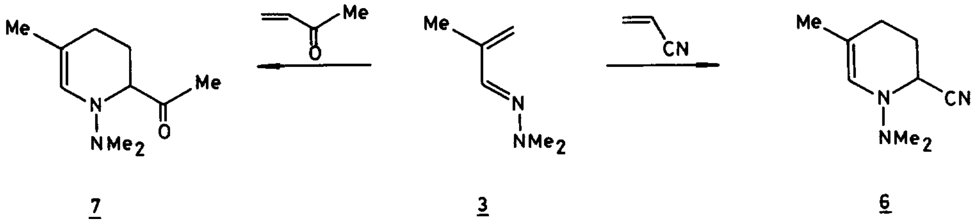
Our approach is based on the well-known capacity of hydrazones to react with electrophilic reagents at either nitrogen or carbon[4]. This is suggestive of an interaction between the lone pair of the nitrogen atom and the π system. This idea is also supported by the bathochromic shift of the conjugated UV band of hydrazones as compared to oximes or simple imines[5]. Thus, we anticipated that the substitution of R in 1 for a dialkylamino group would result (a) in an increased reactivity of the azadiene with respect to electrophilic dienophiles, (b) in a reversal of its "polarity" by increasing the coefficient at C-4 of the highest occupied molecular orbital : α,β-*unsaturated hydrazones 2 should behave as 1-amino-1-aza-1,3-dienes.*

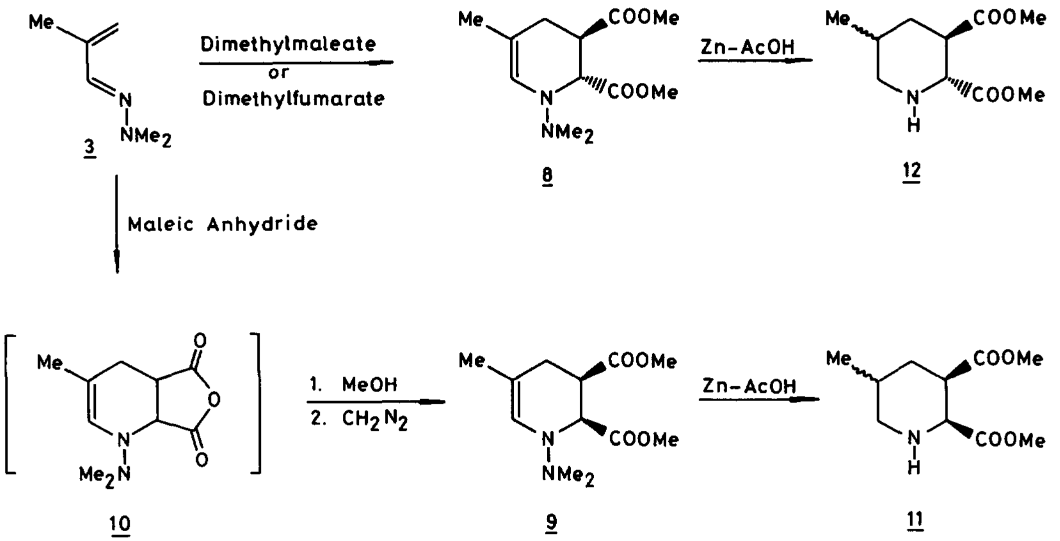
Treatment of the N-dimethylhydrazone 3 (1 eq) derived from methacrolein with naphthoquinone (2 eq) in acetonitrile for 24 hrs produced the aromatized adduct 4 in 92% yield after chromatography on alumina (benzene : ether 80:20)[6,7].



When the reaction was conducted at 20°C in CH_2Cl_2, the unstable primary adduct 5 could be observed by NMR together with some naphthoquinone. *In contrast,* the corresponding oximes did not react with naphthoquinone after prolonged reflux in acetonitrile. Starting materials were recovered unchanged.

That the dimethylamine substituent had reversed the normal "polarity" of the vinyl imine system was demonstrated by the regiochemistry of the reaction. The slow (230 hrs) reaction of equimolar amounts of 3 and acrylonitrile in benzene (sealed tube, 100°C) yielded 53% of a single regioisomer 6 (bulb-to-bulb, 65°C/0.01 Torr). Similarly the cycloaddition of 3 with methylvinylketone (molar ratio 2:1) in acetonitrile (sealed tube, 100°C, 211 hrs) gave the single regioisomer 7 [8]. Detailed analysis of the ^1H and ^{13}C NMR spectra of 6 and 7 confirmed the structural assignments (e.g. 6 ^{13}C NMR, $CDCl_3$, δC_5: 26.83; δC_6: 48.07, $^1JC_6$-H: 147.2 Hz).





Both dimethylmaleate and dimethylfumarate reacted with 3 (molar ratio 1:2, 100°C, 166 hrs with maleate, 138 hrs with fumarate) to give the trans adduct 8. Stereochemical assignment in 8 was based on the value of the coupling constants of the vicinal protons at C_5 and C_6 (J_{trans}= 8 Hz). This was further confirmed by a synthesis of the cis isomer 9 (J_{cis}= 4 Hz) from the reaction of 3 with maleic anhyride (molar ratio 1:1, CH_2Cl_2, 20°C, 30 min.) followed by methanolysis of the adduct 10 and esterification with diazomethane (56% yield from 3).

The synthetic usefulness of these new Diels-Alder reactions rested upon the possibility of removing the often undesirable dimethylamine substituent in the adducts. This was easily achieved, e.g. by reacting 9 for 1 hr at 80°C with three equivalents of zinc in acetic acid. The mixture was then brought to pH 8 with a 10% solution of sodium carbonate. Extraction with CH_2Cl_2 and bulb-to-bulb distillation gave 11 (60%, 60-70°C/0.05 Toor) as a mixture of diastereoisomers. Compound 9 reacted in a similar fashion to give 12 (60%), also as a mixture of diastereoisomers. Until now we have not yet found conditions which cleaved the N-N bond without reducing the carbon-carbon double bond.

Our model experiments suggest a high synthetic potential for the readily available α,β-unsaturated hydrazones. However the scope of the method in terms of structural variations of the dienes has yet to be defined. In particular it would be interesting to examine the reactivity of α,β-unsaturated hydrazones bearing alkoxy or silyloxy substituents at position 3. Work along these lines is currently in progress in our laboratory.

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References and Notes

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4. See, for instance : R.F. Smith and L.E. Walker, J. Org. Chem. 27, 4372 (1962); M. Colonna, Publicaziani Ist. Chimica Universita Trieste 30, 1 (1961); ibid. 34, 1 (1964); P. Bouchet, J. Elguero and R. Jacquier, Bull. Soc. Chim. France 4716 (1967); R. Bhreme and H.E. Nikolajewski, Z. Chem. 8, 226 (1968); Tetrahedron 25, 1159 (1969); ibid 32, 731 (1976); R. Baumes, R. Jacquier, G. Tarrago, Bull. Soc. Chim. France 1147 (1974); 260 (1976); V. Bardakos, W. Sucrow, A. Fehlauer, Chem. Ber. 108, 2161 (1975); H. Suschitzky, R.E. Walrond and R. Hull, J. Chem. Soc. Perkin I 47 (1977); B.B. Snider, R.S.E. Conn and S. Sealfon, J. Org. Chem. 44, 218 (1979); G. Le Fèvre and J. Hamelin, Tetrahedron 36, 887 (1980).
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6. All compounds were fully characterized by Mass, Ir, ^1H and ^{13}C spectroscopies.
7. The oxidation step consumes some naphthoquinone which, therefore should be in excess.
8. An excess of 3 is necessary in order to avoid a [4+2] adduct between 7 and methylvinylketone.

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