Tetrahedron Letters, Vol.27, No.6, pp 699-702, 1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

DIENAMINES AS DIELS-ALDER DIENES. AN EFFICIENT CYCLOHEXANNULATION SEQUENCE.

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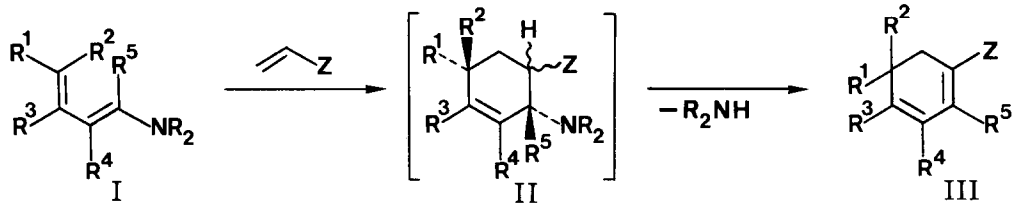
Abstract: An efficient cyclohexannulation sequence is described whose key step involves a *Diels-Alder* reaction between an (E)-dienamine and methyl acrylate.

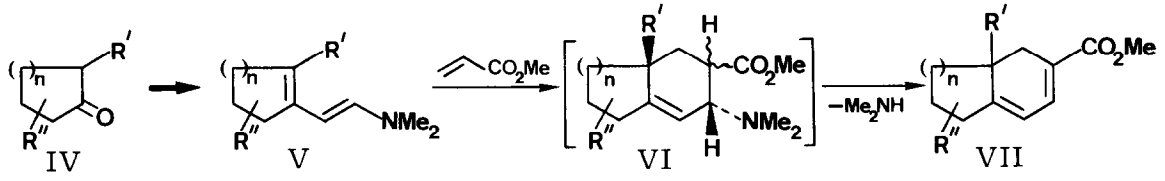
The use of dienamines I as *Diels-Alder* dienes is well documented[1,2]. Main features of their [4+2]cycloadditions with dienophiles are: i) high reactivity, and ii) ability of the dialkylamino group to direct the cycloaddition regiochemistry towards selective formation of cycloadducts II. In addition, subsequent elimination of the secondary amine from II readily affords cyclohexa=dienes III (*cf. Scheme 1*). We now report an application of this transformation (i.e. I → III) in

Scheme 1



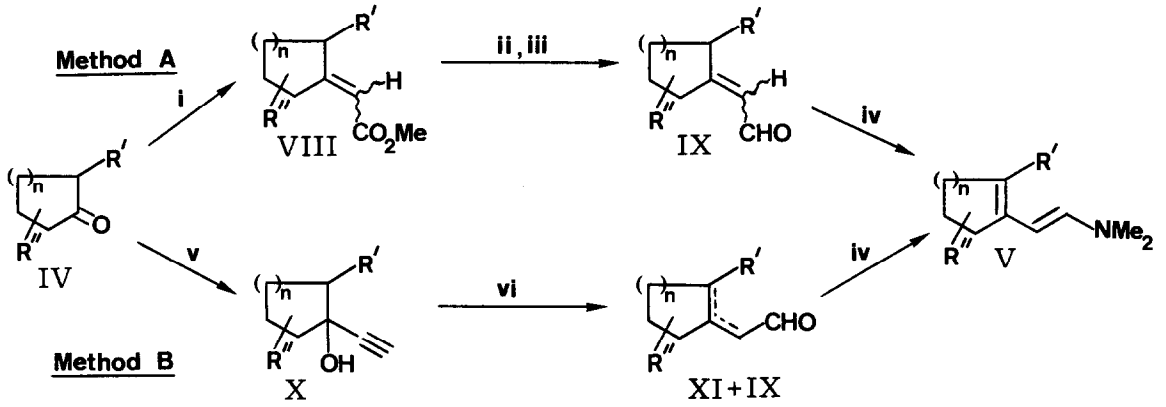
a cyclohexannulation sequence which converts cycloalkanones IV into the bicyclic dienesters VII *via* (E)-dienamines V and the bicyclic cycloadducts VI (*cf. Scheme 2*).

Scheme 2



The (E)-dimethylaminodienes V were prepared from cycloalkanones IV by using one of two methods (*cf. Scheme 3*)[3]. Method A involved the following procedure: *Wadsworth-Emmons* reaction of IV with sodium trimethylphosphonoacetate gave the α,β-unsaturated esters VIII which were con=verted to the aldehydes IX by reduction to the corresponding allylic alcohols followed by oxi=dation with MnO_2. In contrast Method B entailed reaction of IV with sodium acetylide and isomerisation of the resulting acetylenic alcohols X to the α,β- and/or β,γ-unsaturated alde=

Scheme 3

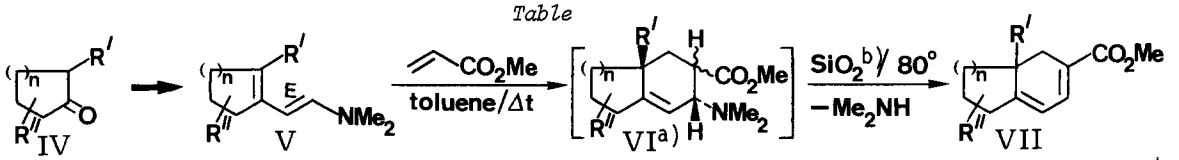


i) $(MeO)_2P(O)CH_2CO_2Me/NaH/THF$; ii) $LiAlH_4/Et_2O$; iii) MnO_2/CH_2Cl_2; iv) 40% aq. $Me_2NH/90^o$; v) Na-≡/THF-toluene; vi) $[(Ph_3SiO)_3V(O)]$/xylene ↑↓.

hydes, IX and XI, using a silylvanadate catalyst[4]. Finally, treatment of IX or XI with 40% aqueous Me_2NH directly afforded the (E)-dimethylaminodienes V. Thus dienamines 10 - 18[5] were prepared from cycloalkanones 1 - 9 in good overall yield (48-66%, *cf. Table*).

The reaction of dienamines 10 - 14 with methyl acrylate (1.5 mole equiv.) in toluene (10% solution) at 100^o during 3 h afforded, with total regioselectivity, two diastereoisomeric cyclo= adducts, VI *cis* and VI *trans*, which result from *endo* and *exo* cycloaddition transition states. Without isolation treatment with silica gel at 80^o resulted in the elimination of Me_2NH and the formation of the bicyclic dienesters 19 - 23 in excellent overall yield (76-86%, *cf. Table:* entries 1-5). In contrast the more substituted dienamines 15 - 18 required more stringent con= ditions (*INOX* autoclave, 150^o/24 h). For 15 and 16 complex mixtures of cycloadducts were obtained which, when treated with silica gel, afforded 57:43 and 20:80 mixtures (82 and 80% yields respec= tively) of the expected dienesters 24 and 26 together with their unexpected positional isomers 25 and 27 (diastereoisomeric mixtures)(*cf.* entries 6 and 8). It is assumed that 25 and 27 result from a facile cycloaddition between methyl acrylate and the dienamines 15a and 16a which are formed by isomerisation of their thermodynamically favoured isomers, 15 and 16 (*cf. Scheme 4*)[6]. Indeed, in agreement with this assumption, effecting the cycloadditions at 100^o during 24 h (*cf.* entries 7 and 9) afforded, after elimination of Me_2NH, 25 and 27 almost exclusively (25:24

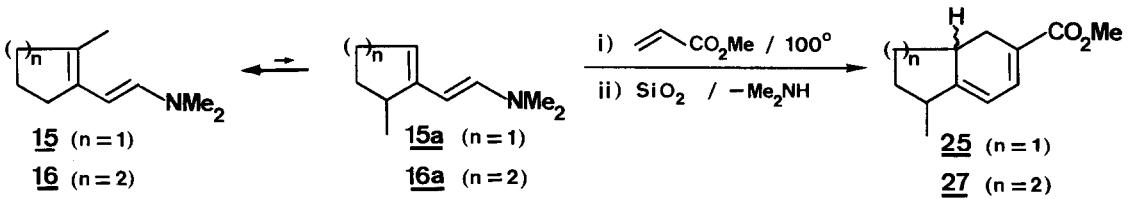
Table



Entry	KETONE	DIENAMINE (PREP. METHOD c), YIELD %)	D.–A. React. Cond.	PRODUCT(S) d,e)	Yield %f)
1	1	10 (n=1) (A,48)		19 (n=1)	81
2	2	11 (n=2) (A,56)	100°/3h	20 (n=2)	83
3	3	12 (n=3) (A,60)		21 (n=3)	86
4	4	13 (A,57)	100°/3h	22	84
5	5	14 (B,57)	100°/3h	23	76
6	6	15 (A,54)	150°/24h	(57 : 43) 24 + 25 (1:1)	82
7			100°/24h	(12 : 88)	83
8	7	16 g) (B,53)	150°/24h	(20 : 80) 26 + 27	80
9			100°/24h	(4 : 96)	84
10	8	17 (B,58)	150°/24h	28 (1:1)	76
11	9	18 (B,66)	150°/24h	29 (m.p.41-2°)	84

a) Diastereoisomeric mixture, analysis by GC/MS coupling; the presumed stereochemistry of VI is consistent with the ^{1}H-NMR (360 MHz, $CDCl_3$) spectral data, e.g. entry 5, major isomer (52%): δ1.01, 1.10 (2 *s*, CH_3); 2.30 (*s*, $N(CH_3)_2$); 3.69 (*s*, CO_2CH_3); 5.54 (*d*, *J* = 4 Hz, H-C(4)); minor isomer (48%): δ1.04, 1.08 (2 *s*, CH_3); 2.28 (*s*, $N(CH_3)_2$); 3.68 (*s*, CO_2CH_3); 5.36 (br.*s*, H-C(4)); b) 2 xg SiO_2 (0.06 - 0.2 mm (*Merck*)) for xg VI, reaction time: 2 → 6 h; c) *cf. Scheme 3*; d) all new compounds have been fully characterised spectroscopically, *e.g.* 23: IR(film): 1700, 1564, 1426, 1240, 740 cm^{-1}; UV(EtOH): λmax. 306 nm (ε 11,700); ^{1}H-NMR(360 MHz, $CDCl_3$): δ1.06, 1.15 (2 *s*, 6 H); 1.20 - 1.70 (5 H); 1.93 (*m*, 1 H); 2.02 (*m*, 1 H); 2.53 (*m*, 1 H); 2.73 (*dd*, *J* = 16, 9 Hz, 1 H); 3.74 (*s*, 3 H); 5.90 (*m*, H-C(4)); 6.94 (*m*, H-C(3)); ^{13}C-NMR(90.5 MHz, $CDCl_3$); 168.0 (*s*), 158.3 (*s*); 134.0 (*d*), 123.8 (*s*), 115.0 (*d*), 51.4 (*q*), 41.0 (*t*), 36.5 (*s*), 35.9 (*t*), 33.6 (*d*), 29.9 (*t*), 28.8 (*q*), 28.2 (*q*), 21.5 (*t*); MS: 220 (34, M^+), 163 (30), 150 (100), 105 (50); e) m.p. of corresponding carboxylic acid (VIIa): 19a 176°, 20a 139°, 21a 154°, 22a 131°, 23a 138°, 29a 154°; f) yields refer to chromatographically pure distilled products; g) 4:1 mixture of 1'- and 6'-cyclohexenyl double bond isomers.

Scheme 4



(88:12) and 27:26 (96:4)). With 17 as substrate (*cf.* entry 10) a mixture of four cycloadducts was obtained which subsequently gave, after treatment with silica gel, 28 as a 1.2:1 mixture of diastereoisomers (76% yield). Finally, 18[7] afforded a 57:43 mixture of cycloadducts which, after elimination of Me_2NH, furnished 29 in 84% yield (*cf.* entry 11).

The chemistry of these novel dienesters 19 - 29 is currently under study and, in addition, further cycloadditions of dienamines 10 - 18 with other dienophiles are being investigated. In this context the following letter describes a novel benzannulation sequence in which the *Diels-Alder* reaction of a dienamine with methyl propiolate constitutes the key step.

References and Notes

[1] For a review of dienamines as *Diels-Alder* dienes, see: M. Petrzilka & J.I. Grayson, *Synthesis*, 753 (1981); see also: Y. Chrétien-Bessière & H. Leotte, *C.R. Séances Acad. Sci.* 255, 723 (1962); H. Leotte, *Rev.Port.Quim.* 7, 214 (1965); for a recent intramolecular version, see: T.-C. Wu & K.N. Houk, *Tetrahedron Lett.* 26, 2293 (1985).

[2] For a general review on conjugated enamines, see: P.W. Hickmott, *Tetrahedron* 40, 2989 (1984).

[3] Methods A and B are complementary in the sense that nucleophilic attack of sodium trimethylphosphonoacetate, compared to sodium acetylide, is more sensitive to steric hindrance at the cycloalkanone carbonyl group.

[4] H. Pauling, D.A. Andrews & N.C. Hindley, *Helv.Chim.Acta* 59, 1233 (1976).

[5] Dienamines 10 - 18 (E/Z ⩾30:1) are readily distillable, pale-yellow oils which may be stored at -30° without appreciable decomposition.

[6] This isomerisation, possibly catalysed by traces of H_2O, presumably proceeds *via* the β,γ- and α,β-unsaturated aldehydes **XI** and **IX**.

[7] For the construction of the drimane skeleton using 18 as a *Diels-Alder* diene, see: R.L. Snowden, *Tetrahedron Lett.* 25, 3835 (1984).

(Received in France 5 December 1985)