A New 2-Aminobuta-1,3-diene Derivative and its Utility as a Building Block in Hetero- and Carbo-cyclization Processes

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2-Morpholinobuta-1,3-diene cycloadds to aromatic aldehydes, *N*-benzylideneaniline, and methyl vinyl ketone, to give oxan-4-ones, 4-morpholinotetrahydropyridines, and 4-acetyl-1-morpholinocyclohexene derivatives, respectively, with a high degree of diastereoselectivity.

We have recently reported an easy and regioselective preparation of 2-morpholinobuta-1,3-dienes.[1] These systems, almost unknown in the literature, can be considered as 'super-enamines' according to Hickmott's terminology,[2] since they behave as C-β highly reactive enamines. This behaviour agrees with previous MINDO/3 theoretical calculations,[3] which clearly predict for 2-aminobuta-1,3-dienes an almost total inability to act as diene components in [4 + 2]cycloaddition reactions.[4] This fact is in striking contrast to the great reactivity of 2-siloxybuta-1,3-dienes in carbo-[5] and, particularly, hetero-cyclization[6] processes.

We report here the first examples showing the ability of 2-methyl-1-methoxymethyl-3-morpholinobuta-1,3-diene (**1**), obtained *via* catalytic aminomercuriation† of the commercially available (*E*)-3-methylpent-2-en-4-yn-1-ol, to cycloadd to some conventional dienophiles, *e.g.*, aromatic aldehydes, *N*-benzylideneaniline, and methyl vinyl ketone.

The reaction of (**1**) with aldehydes (**2**) and $MgBr_2{\cdot}Et_2O$‡ as Lewis acid (molar ratio 1:2:2; room temperature, 12 h), followed by hydrolysis with 50% aqueous acetic acid, led to a single diastereoisomer of each of the oxan-4-ones (**3**) illustrated in Scheme 1.§ The stereochemistry of (**3**) was deduced from ^{1}H n.m.r. (300 MHz) data;¶ nuclear Overhauser enhancement experiments reveal a *cis*-relationship between C(2)-H and C(6)-H. Compounds (**4**)¶ and (**5**)¶ were formed (74 and 85%, respectively) when the crude reaction product was hydrolysed with a AcONa–AcOH buffer solution (pH 4.6) or aqueous 3M hydrochloric acid, respectively.

The diene (**1**) also reacts with *N*-benzylideneaniline (**6**) in the presence of $ZnCl_2$ as Lewis acid (same reaction conditions as above‡), to give the tetrahydropyridine (**7**) (52%, recrystallized from ethanol; m.p. 147—149 °C)¶ (Scheme 2). The stereochemistry of the single diastereoisomer formed (**7**) has

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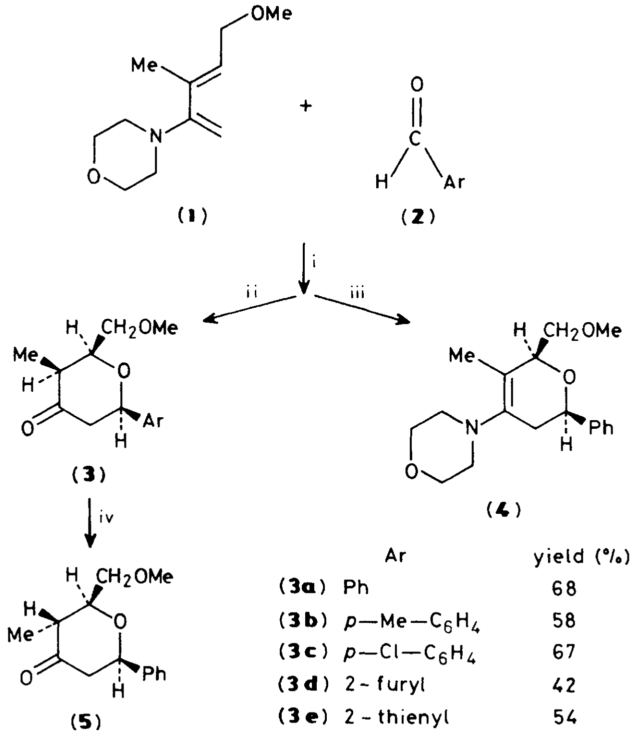
† Same method as in ref. 1; reaction time 24 h; yield, 69%.

‡ The nature of the Lewis acid and the molar ratio of Lewis acid: reagents play an important role in this process: best results were obtained using a twofold excess of both Lewis acid and dienophile.

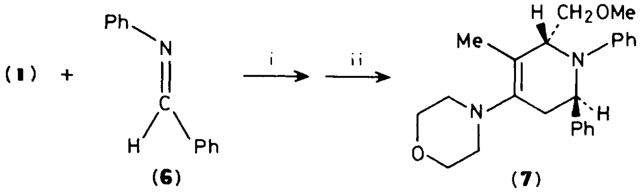
§ When the amino-dienes 1-(cyclohex-1-enyl)-1-*N*-morpholinoethene and 1-(cyclopent-1-enyl)-1-*N*-morpholinoethene were used, a complex mixture was formed, in which no cyclised compounds could be detected.

¶ Elemental analyses and spectroscopic data were in agreement with the structures assigned.

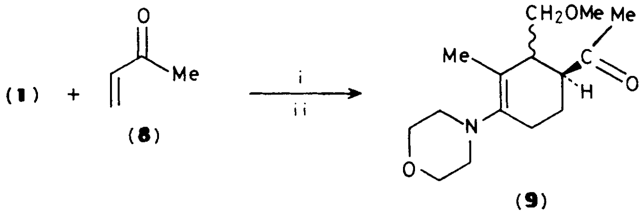


	Ar	yield (%)
(3a)	Ph	68
(3b)	p—Me—C_6H_4	58
(3c)	p—Cl—C_6H_4	67
(3d)	2-furyl	42
(3e)	2-thienyl	54

Scheme 1. *Reagents and conditions*: i, $MgBr_2 \cdot Et_2O$, THF, room temp., 12 h; ii, 50% aqueous AcOH, room temp., 1 h; iii, aqueous AcONa–AcOH (pH 4.6), room temp., 1 h (Ar = Ph); iv, aqueous 3 M HCl, room temp., 12 h (Ar = Ph).



Scheme 2. *Reagents and conditions*: i, $ZnCl_2$, THF, room temp., 12 h; ii, saturated aqueous $NaHCO_3$ solution.



Scheme 3. *Reagents and conditions*: i, $MgBr_2 \cdot Et_2O$, THF, room temp., 12 h; ii, aqueous AcONa–AcOH (pH 4.6), room temp., 1 h.

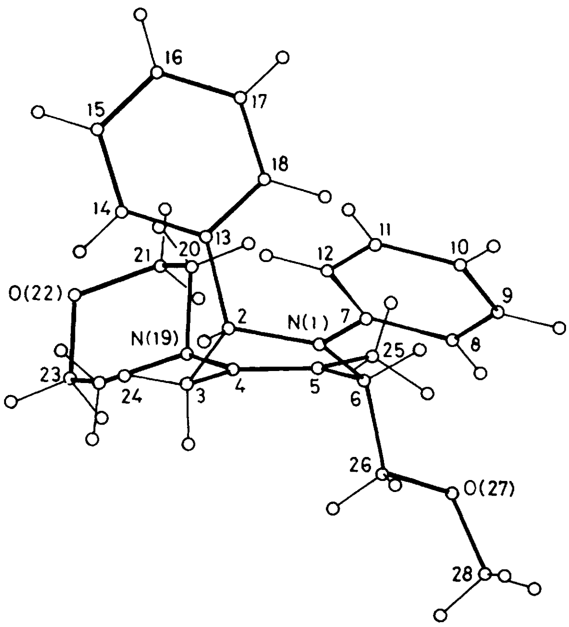


Figure 1. One of the two enantiomeric molecules present in the crystal structure, with the atomic numbering used in the crystallographic analysis, and the crowding of substituents. Lengths (Å) and torsion angles (°): N(1)–C(7) 1.394(3), N(19)–C(4) 1.423(3); C(4)–C(3)–C(2)–N(1) −56.7(2), C(4)–C(3)–C(2)–C(13) +70.0(2), C(4)–C(3)–C(2)–H(2) −173(1); O(27)–C(26)–C(6)–N(1) −107.4(2), O(27)–C(26)–C(6)–C(5) +75.3(2), O(27)–C(26–C(6)–H(6) −42(1); C(6)–N(1)–C(2)–H(2) +140(1), C(6)–N(1)–C(2)–C(3) +23.7(2); C(4)–C(5)LC(6)–H(6) −153(1), C(4)–C(5)–C(6)–N(1) −34.8(3); H(2)–H(12) 2.23(3), H(3a)–H(24a) 2.23(4), H(6)–H(8) 2.09(4), H(8)–H(26b) 2.25(3).

been proved by *X*-ray diffraction (Figure 1).†† The configurational values.[7,8] confirm the structural formula in Scheme 2, as the *trans*-situation of H-2 *vs.* H-6‡‡ can be established just from a MULTAN output. The stereochemical result is consistent with a [4 + 2]cycloaddition process in which a diene–dienophile–catalyst complex, such as that shown in Figure 2, would be involved.[9]

Furthermore, methyl vinyl ketone (**8**) is able to cycloadd to (**1**) in the presence of $MgBr_2 \cdot Et_2O$ as Lewis acid (same reaction conditions as above). Hydrolysis (pH 4.6) of the resulting mixture affords the enamine (**9**) (62%) with 96% diastereoisomeric purity (300 MHz ^{1}H n.m.r.)¶ (Scheme 3).

In a typical run, to an ice-cooled solution of (**2**) or (**8**) (20 mmol) and $MgBr_2 \cdot Et_2O$ (20 mmol) in anhydrous tetrahydrofuran (THF) (60 ml) was slowly added (20 min), under argon, a THF solution (5 ml) of (**1**) (10 mmol). The mixture was allowed to warm to room temperature, and stirred overnight; the resulting mixture was hydrolysed with either 50% aqueous AcOH (10 ml; 1 h) or aqueous AcONa–AcOH (pH = 4.6; 10 ml; 1 h), extracted with ether, and the extract was concentrated under reduced pressure. Compounds (**3**) were purified by high-vacuum distillation, and (**9**) by stirring with hexane. [*E.g.* (**3a**), ^{1}H n.m.r. ($CDCl_3$, 200 MHz): δ 1.20 (d, 3H), 2.41—2.80 (br. m, 3H), 3.34 (s, 3H), 3.47 (dd, 1H), 3.62 (dd,

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†† *Crystal data*: $C_{24}H_{30}N_2O_2$, M = 378.51, colourless prisms, monoclinic, space group $P2_1/c$, a = 9.6374(2), b = 10.6783(2), c = 20.0036(7) Å, β = 95.154(2)°, U = 2050.3 (1) Å^3, Z = 4, D_c = 1.226 g cm^{-3}; F(000) = 816, μ = 5.77 cm^{-1}. 3475 Independent reflections were measured with graphite-monochromated Cu-K_α radiation on a Philips PW 1100 diffractometer (ω–2θ scans). 2812 Reflexions with $I > 3\sigma(I)$ were used in the solution (MULTAN) and refinement (least squares) to R = 0.048, R_w = 0.051. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

‡‡ As [C(6)–N(1)–C(2)–H(2)]–[C(6)–N(1)–C(2)–C(3)] is *ca.* + 120° below the ring plane and [C(4)–C(5)–C(6)–H(6)]–[C(4)–C(5)–C(6)–N(1)] is *ca.* −120 °C above the ring plane, that is, the other side of the ring.

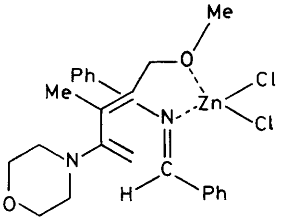

Figure 2

1H), 3.99 (ddd, 1H), 4,66 (dd, 1H), 7.33 (m, 5H). ^{13}C n.m.r. ($CDCl_3$, 50 MHz): δ 9.57 (q), 44.81 (t), 45.48 (d), 57.87 (q), 70.89 (t), 76.35 (d), 77.51 (d), 124.44 (d), 126.68 (d), 127.28 (d), 139.82 (s), 208.04 (s). M.s.: *m/z* 234 (M^+)]. [(**9**), ^{1}H N.m.r. ($CDCl_3$, 200 MHz): 2.10—2.25 (m, 4H), 2.14 (s, 3H), 2.48—2.81 (br. m, 6H), 3.04—3.39 (br. m, 2H), 3.11 (s, 3H), 3.66 (t, 4H). ^{13}C n.m.r. ($CDCl_3$, 50 MHz): δ 16.25 (q), 18.67 (t), 20.90 (t), 27.91 (q), 42.63 (d), 48.74 (d), 49.35 (t), 57.19 (q), 66.38 (t), 71.05 (t), 121.11 (s), 142.04 (s), 208.21 (s). M.s.: *m/z* 276 (M^+)]. (**7**): The foregoing procedure was followed, using $ZnCl_2$ (2.73 g, 20 mmol), and *N*-benzylideneaniline (3.62 g, 20 mmol). After hydrolysis of the reaction mixture with saturated aqueous $NaHCO_3$ solution, the excess of (**6**) was removed by stirring with hexane, and (**7**) recrystallized from ethanol (yield, 52%). [^{1}H n.m.r. ($CDCl_3$, 200 MHz): δ 1.95 (d, 3H), 2.12 (t, 4H), 2.55 (dd, 1H), 2.73 (m, 1H), 3.38 (s, 3H), 3.51 (m, 5H), 3.76 (dd, 1H), 4.38 (dd, 1H), 5.02 (dd, 1H), 6.63 (m, 3H), 7.10 (m, 7H). ^{13}C n.m.r. ($CDCl_3$, 20 MHz): δ 15.4 (q), 29.0 (t), 47.7 (t), 56.6 (d), 57.6 (d), 57.8 (q), 65.6 (t), 73.7 (t), 111.7 (d), 114.7 (d), 124.9 (d), 125.0 (d), 125.1 (s), 126.4 (d), 127.3 (d), 136.9 (s), 142.3 (s), 144.8 (s). M.s.: *m/z* 379 ($(M + 1)^+$)].

Received, 9th February 1988; Com. 8/00440D

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