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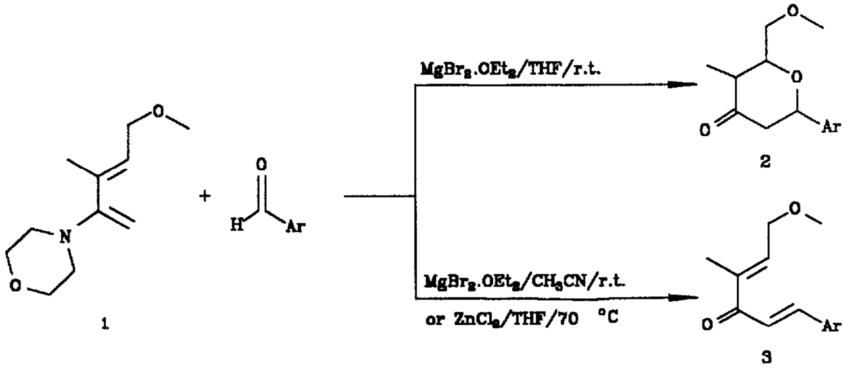
2-MORPHOLINOBUTADIENES AS SYNTHON FOR THE REGIOSELECTIVE PREPARATION OF 3-MORPHOLINO-1,4-PENTADIENES AND β-HYDROXYVINYLKETONES

José Barluenga,* Fernando Aznar, Mª Paz Cabal and Carlos Valdés
Departamento de Química Organometálica, Universidad de Oviedo
33071 Oviedo, Spain

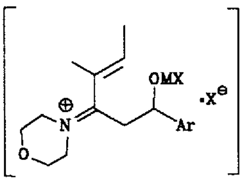
Summary: A very simple regioselective preparation of 3-morpholino-1,4-pentadienes and β-hydroxyvinylketones is described.

2-Morpholinobutadienes are easily prepared in a multigram-form by catalytic aminomercuriation of en-ynes.[1] From the point of view of their chemical reactivity, they can act as simple enamines or participate as dienes in [4+2] cycloaddition processes. This different behaviour depends not only on the type of substituents attached to the 2- morpholinobutadiene [2]but also on the Lewis acid and solvent used. In this context, the reaction of **1** with aromatic aldehydes in the presence of $MgBr_2.OEt_2$ in THF affords exclusively 4-oxanone derivatives **2**.[3] On the other hand, when $ZnCl_2$ in CH_2Cl_2 or $MgBr_2.OEt_2$ in CH_3CN are used as Lewis acid, divinylketones **3** are the only product obtained[4], *Scheme I.*

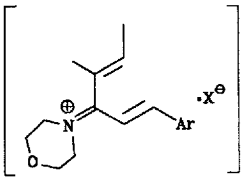
Scheme I



It seems reasonable to think that intermediates **A** and/or **B** are involved in the formation of **3**. If an intermediate *type* **B** operates, its simple reduction reaction should give 3-morpholino-1,4-pentadienes **6**.



A



B

Thus, sequential treatment of 2-morpholinobutadienes **4** with a variety of aromatic aldehydes **5** in the presence of $MgBr_2.OEt_2$ (*Method A*) or $ZnCl_2$ (*Method B) (see Table I*) followed by reduction with $NaBH_4/MeOH$ afforded after aqueous work-up, 3-morpholino-1,4-pentadienes **6** in good yields, *Scheme II, Table I.*

Scheme II

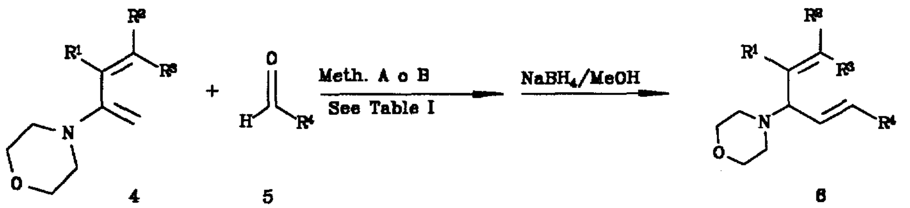


Table I. Preparation of 3-morpholine-1,4-butadienes from 2-morpholinobutadienes.

Compound	R^1	R^2	R^3	R^4	Method[a] A or B	Yield[b] %
6a	CH_3	CH_2OCH_3	H	Ph	A	64
6b	CH_2CH_3	H	CH_3	Ph	B	55
6c		$-(CH_2)_4-$	H	Ph	A	68
6d		$-(CH_2)_4-$	H	p-Cl-Ph	A	56
6e	CH_3	CH_2OH	H	p-Cl-Ph	A	75

a) Method A **4**:**5**: $MgBr_2.OEt_2$ (molar ratio 1:2:2, CH_3CN, 25°C, 6h). Method B **4**:**5**:$ZnCl_2$ (molar ratio 1:2:2, THF, 70°C, 8h).
b) Isolated yield after *trap to trap* high vacuum condensation (10^{-5} Torr) . All the new compounds were characterized by high resolution NMR analysis.

These results show that the formation of the double bond to give the divinylketones occurs before hydrolysis (*type* **B**). However, when the reaction of **4** with different aromatic or aliphatic aldehydes was carried out in the presence of $TiCl_4$ as a Lewis acid, after hydrolysis, it furnishes β-hydroxyvinylketones **7** in a good yield, *Scheme III, Table II.* It is worth pointing out, that when R^2 = $CH_2OSi(CH_3)_3$ in the same reaction conditions, hydrolysis of the silicon - oxygen bond occurs and dihydroxyvinylketones **8** are formed directly, *Scheme III, Table II.* When **1** (R^1 = CH_3, R^2 = CH_2OCH_3, R^3 = H) is treated with benzaldehyde and $TiCl_4$ followed by $NaBH_4/MeOH$ reduction, the unsaturated morpholinoalcohol **9** were formed as a diastereoisomeric mixture, *Scheme III, Table II.* It permits us to conclude that in this case the intermediate which operates is one of *type* **A.**

Scheme III

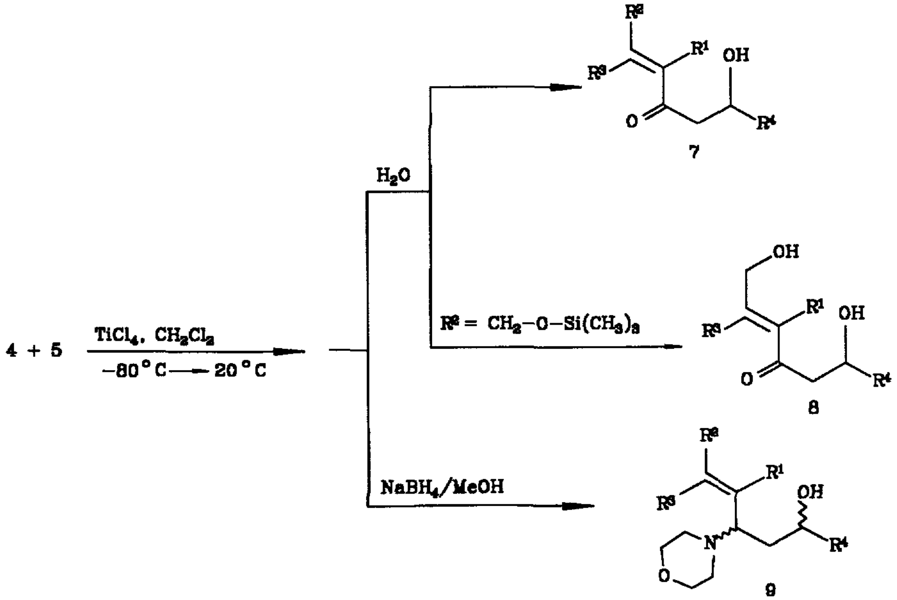


Table II: Hydroxyvinylketones prepared.

Compound	R^1	R^2	R^3	R^4	Yield[a] %
7a	CH_3	CH_2OCH_3	H	Ph	68
7b	CH_3	CH_2OCH_3	H	p-Cl-Ph	64
7c	-$(CH_2)_4$-		H	Ph	57
7d	CH_3	CH_2OCH_3	H	^{i}Pr	69
7e	CH_3	CH_2OCH_3	H	^{n}Pr	71
7f	CH_3	H	H	Ph	74
8a	CH_3	CH_2OH	H	Ph	67
8b	CH_3	CH_2OH	H	^{n}Pr	64
8c	CH_3	CH_2OH	H	$CH=CHCH_3$	54

a) Isolated yield after *trap to trap* high vacuum condensation (10^{-5} Torr). All the new compounds were characterized by high resolution NMR analysis.

In conclusion, the easily avaliable 2-morpholinobutadienes are good starting material for the obtention not only of 4-oxanones or divinylketones but also for the preparation in a regioselective way of 3-morpholino-1,4-pentadienes and β-hydroxyvinylketones.

Experimental:

General Procedure for the Preparation of 3-morpholino-1,4-pentadienes 6.

Method A: A solution of 2-morpholinobutadiene **4** (10 mMol) in 10 ml of dry CH_3CN was slowly added to a solution of $MgBr_2.Et_2O$ (20mMol, 5.56 g) and an aromatic aldehyde (20 mMol) under an argon atmosphere in dry CH_3CN.

Method B: The procedure is identical with that for *method A* but employing dry THF as solvent and $ZnCl_2$ as catalyst. The reaction was carried out at 70°C.

The reaction mixture was stirred for 6 h and then 10 ml of MeOH and 0.5 g of $NaBH_4$were added succesively. After 2 h, it was hydrolised with 50 ml of NaOAc/HOAc buffer solution (pH = 4.6). The organic layers were separated by *acid basic* work up. Removal of the solvents in the basic phase afforded 3-morpholino-1,4-pentadiene as a very pure product which can be condensed in high vacuum (10^{-5} Torr).

Spectral data: E.g. for ***N*-[4-methoxy-2-methyl-1-(2-phenylethenyl)-2-butenyl]morpholine (6a).** ^{13}C-NMR ($CDCl_3$) δ = 138.4 (s), 136.1 (s), 131.7 (d), 128.4 (d), 127.8 (d), 126.8 (d), 126.0 (d), 125.7 (d), 76.7 (d), 67.8 (t), 66.2 (t), 56.9 (q), 51.2 (t), 12.3 (q) ppm.[5] ^{1}H-NMR ($CDCl_3$/TMS) δ = 7.4-7.1 (m,5H), 6.4 (d,1H), 6.1 (dd,1H), 5.5 (dd,1H), 3.9 (d,2H), 3.6 (t,4H), 3.2 (s,3H), 3.0 (d,1H), 2.5-2.3 (m,4H), 1.67 (s,3H) ppm.[5]

General Procedure for the Preparation of Hydroxyvinylketones 7 and 8.

The procedure is identical with that for *methods A* and *B* but employing dry CH_2Cl_2as solvent and $TiCl_4$ as catalyst. The reaction was carried out at -80°C. After 6 h, the reaction mixture was hydrolised with 50 ml of H_2O and stirred for 2 h. Then, extracted with Et_2O and dryed over Na_2SO_4. Removal of the solvents afforded β-hydroxyvinylketones **7** and **8** which were condensed in high vacuum (10^{-5} Torr).

Spectral data: E.g. for **6-hydroxy-1-methoxy-3,7-dimethyl-2-octen-4-one (7d).** ^{13}C- NMR ($CDCl_3$) δ = 201.4 (s), 138.9 (d), 137.1 (s), 71.9 (d), 69.2 (t), 58.1 (q), 40.2 (t), 32.7 (d), 18.0 (q), 17.2 (q) ppm[5] ^{1}H-NMR ($CDCl_3$/TMS) δ = 6.6 (t,1H), 4.1 (d,2H), 3.7 (m,1H), 3.2 (s,3H), 2.8-2.6 (m,2H), 1.7-1.5 (m,1H), 1.3-0.8 (m,9H) ppm.[5]

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