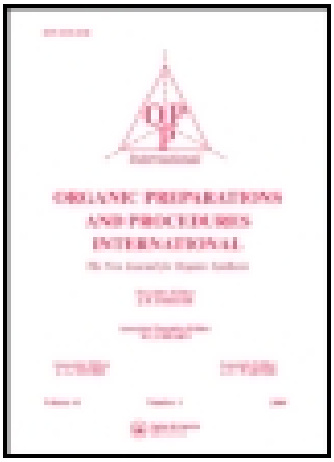

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Dario Lazzari [a] , Mirco Rossi [a] , Massimo Soverini [a] , Marco Mazzega [b] & Ottorino De Lucchi [b]

[a] Ciba Specialty Chemicals S.p.A. Additives , via Pila 6/3, I-40044, Pontecchio Marconi, Bologna, ITALY

[b] Dipartimento di Chimica , Università di Venezia , Dorsoduro 2137, I-30123, Venezia, ITALY

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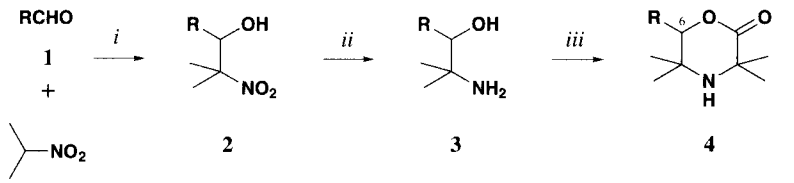
SYNTHESIS OF 3,3,5,5-TETRAMETHYLMORPHOLINONES FUNCTIONALIZED AT THE 6-POSITION

Dario Lazzari*†, Mirco Rossi†, Massimo Soverini†,
Marco Mazzega†† and Ottorino De Lucchi*††

† *Ciba Specialty Chemicals S.p.A. Additives, via Pila 6/3, I-40044 Pontecchio Marconi, Bologna, ITALY*
†† *Dipartimento di Chimica, Università di Venezia, Dorsoduro 2137, I-30123 Venezia, ITALY*

The utility of 3,3,5,5-tetramethylmorpholinone (**4a**) as light stabilizer (HALS)[1] and as precursor of multipurpose nitroxides[2] is well established. Since the only position of the heterocycle left available for functionalization is the 6-position, the possibility of attaching a substituent at this end is of interest in view of the practical applications of these molecules, especially if the substituent is a reactive functional group able to graft the tetramethylmorpholinone to a desired polymer or material, or to an insoluble bed for the preparation of heterogeneous reagents. With the aim of producing this type of molecule, we applied reactions that are quite effective for the parent compound **4a** (Eq 1)[3] to properly substituted substrates; however, we became quickly aware that what is valid for the parent system **4a** is not adaptable to the more complex substrates **4b** and **4c**. Here, we describe the synthesis of morpholinones **4b** and **4c** bearing an acetal and an alkene group at the 6 position. Whilst the preparation of **4b** entailed a procedure adapted from that of the parent system **4a**, the preparation of **4c** required an alternative approach.



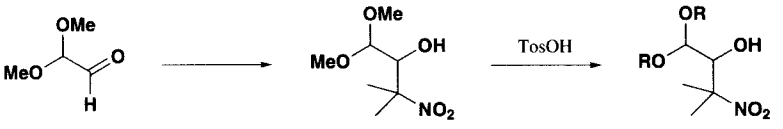
(1)

a) R = H **b**) R = $CH(OMe)_2$ **c**) R = $CH_2CH{=}CH_2$

i) NaOH, H_2O, Aliquat *ii*) H_2, Raney-Ni (for **2a**); HCO_2NH_4, Pd/C (for R = **2b**) *iii*) $CHCl_3$, NaOH, acetone

Henry reaction of 2,2-dimethoxyethanal (or the ethoxy analogue) with 2-nitropropane in a two-phase system, following the procedure developed by Ballini *et al.*[4] afforded good yields

of adduct **2b**. The use of the commercially available solution of glyoxal 1,1-dimethylacetal in *t*-butyl methyl ether (MTBE) is convenient from a practical viewpoint even though the reaction required a longer period of time compared to runs carried out using the relatively unstable pure material.



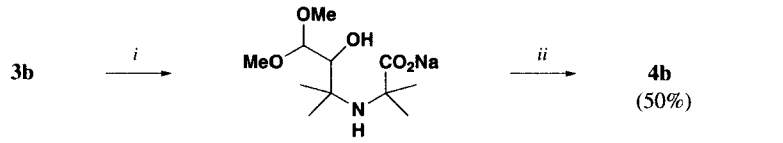
(2)

2b

5 R = R = CH_2Ph
6 R-R = CH_2-CH_2
7 R-R = CHPh-CHPh (racemic)

Transacetalyzation of **2b** with benzyl alcohol, ethylene glycol as well as with racemic hydrobenzoin (PhCH(OH)CH(OH)Ph) led to acetals **5-7** in fair to good yields. The latter compound (**7**), which might prove useful for the preparation of chiral non-racemic products,[2] was an approximate 1:1 mixture of diastereoisomers.

Reduction of the nitro group of **2b** to the required amino group of **3b** under the reaction conditions which are highly efficient with the parent system,[5] proved ineffective; H_2 with Pd/C (5%) or Raney-Ni, Zn/HCl, Fe/HCl, $RuCl_2(PPh_3)_3/H_2$ as well as other reducing agents gave complex reaction mixtures and/or retro Henry reaction to produce the starting nitropropane and aldehyde. Reasoning that the retroaldol reaction was the main problem based on similar literature observations,[6] we protected the alcohol **2b** as its trimethylsilyl ether and carried out the reduction on the protected system,[6] still with no success. Eventually, the reduction was achieved by the method of Barrett and Spilling (Eq 1),[7] in high yields without detectable side-reactions.



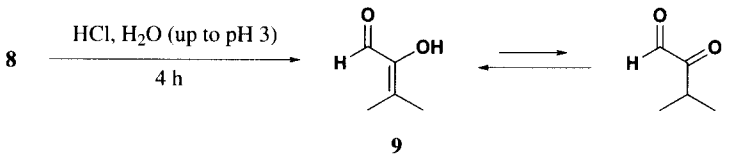
(3)

8 (50%)

i) Me2CO, CHCl3, NaOH *ii*) 1. HCl, H2O (up to pH 3) 2. Et3N, toluene, reflux

The cyclization step was carried out following the Lai protocol[3] to produce compound **8** in ca. 50% yield. Salt **8** is a stable solid that could be isolated as a mixture with unreacted NaOH and NaCl formed in the reaction mixture. Concomitant with the production of **4b** in the last step of Eq 3 was the formation of enol **9**. The latter compound probably arose from decomposition of the acetal function of **8** prior to cyclization to morpholinone **4b**, as **4b** proved stable under the reaction conditions that otherwise transform **8** into **9** in high yields (Eq 4). The formation of enol **9** is noteworthy because the literature reports only on its keto-tautomer.[8] The formation of the only enolic form was confirmed by the ^1H NMR which displayed the aldehydic proton (9.78 ppm) and the ^{13}C NMR spectrum showing the carbonyl group at 183.25 ppm and two vinyl

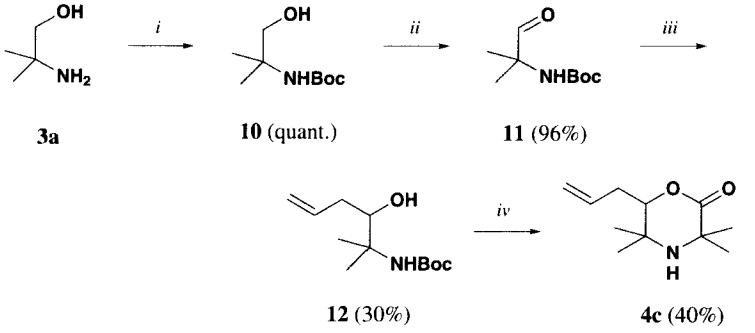
carbons at 145.25 and 131.22 ppm. The stability of enol **9** may be ascribed to an intramolecular hydrogen bond.



(4)

9

Due to the low yield of **4b**, we sought other 6-functionalized 3,3,5,5-tetramethylmorpholinones and entertained the preparation of **4c** following the reaction sequence shown in Eq 5. It should be noted that this route does not require the crucial reduction of the β-nitro alcohol, necessary in the preparation of **4b** described in Eq 1.



3a **10** (quant.) **11** (96%)

12 (30%) **4c** (40%)

(5)

i) Boc_2O, CH_2Cl_2 (Ref. 9) *ii*) DMSO, $(COCl)_2$ (Ref. 9) *iii*) CH_2=$CHCH_2SiMe_3$, $TiCl_4$
iv) 1. HCl, AcOEt 2. Me_2CO, $CHCl_3$, NaOH 3. HCl, H_2O 4. Et_3N, Toluene

Commercial **3a** was Boc-protected to produce **10** quantitatively as a colorless, stable, crystalline compound that was submitted to Swern oxidation to produce **11** in high yields as reported.[9] Unfortunately, the reactivity of this aldehyde proved very poor toward standard organometallic reagents (Grignard and organolithium compounds). In contrast, Lewis acid catalysed allylation of **11** with trimethylsilylpropene[10] afforded only fair but consistent yields of the desired alcohol **12**. Deprotection and Lai cyclisation[3] delivered the target molecule **4c** in 40% yield (overall yield ca. 13% from **3a**).

In conclusion, in this work we have devised synthetic procedures for the preparation of 6-substituted 3,3,5,5-tetrasubstituted morpholinones that may find useful practical applications in organic synthesis and in industry.

EXPERIMENTAL SECTION

Reactions were performed with standard techniques using reagents as purchased by the chemical suppliers or purified to match reported physical data and monitored by TLC or ^{1}H-NMR. ^{1}H NMR and ^{13}C-NMR spectra were recorded on a Bruker AC200 using TMS as internal standard. IR spectra were collected on a BIO-RAD FTS-40. Mass spectra were obtained with a Hewlett-Packard 5890-II instrumentation. Microanalytical data were performed in house.

1,1-Dimethoxy-3-nitro-3-methylbutan-2-ol (2b).- To a solution of 2-nitropropane (4.5 mL, 50 mmol), Aliquat (2.25 mL, 5 mmol) and NaOH (150 mL of a 0.025 M solution) was added a MTBE solution of 2,2-dimethoxyethanal (10 mL of a ca. 45% wt solution, ca. 50 mmol) at 0°. After 36 h, brine (20mL) was added to the reaction mixture and extracted with ether (4 x 30 mL). The organic phase was dried ($MgSO_4$) and vacuum concentrated to an oil: 8.6 g (90% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.33 (1 H, d, *J* = 5.6 Hz), 4.11 (1 H, dd, *J* = 5.6, 4.6 Hz), 3.45 (3 H, s), 3.40 (3 H, s), 2.64 (1 H, d, *J* = 4.6 Hz), 1.62 (3 H, s), 1.59 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 103.07, 89.39, 74.39, 54.76, 54.62, 22.52, 22.49. The product was used in the next step without further purification.

1,1-Dibenzyloxy-3-nitro-3-methylbutan-2-ol (5).- A solution of 1,1-dimethoxy-3-nitro-3-methylbutan-2-ol (**2b**) (1.93 g, 10 mmol), benzyl alcohol (2.58 mL, 25 mmol) and *p*-toluenesulfonic acid (190 mg, 1 mmol) in anhydrous dichloromethane (25 mL) was refluxed into a Soxhlet apparatus charged with 15 g 3Å molecular sieves. After 36 h at reflux, potassium bicarbonate (1 g in 10 mL) was added and the reaction mixture extracted with dichloromethane (3 x 10 mL). After standard work up, 2.24 g of a colorless oil was obtained (65% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.48-7.28 (10 H, m), 4.78-4.55 (5 H, m), 4.27 (1 H, t, *J* = 5.3 Hz), 2.75 (1 H, d, *J* = 5.3 Hz), 1.59 (3 H, s), 1.56 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 136.81, 136.71, 128.64, 128.56 128.19, 128.09, 128.05, 128.03, 127.93, 127.85, 99.98, 89.51, 74.91, 69.17, 69.09, 22.64, 22.41. *Anal.* Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 66.00; H, 6.37; N, 3.88

1-(1,3-Dioxolan-2-yl)-3-nitro-3-methylbutan-2-ol (6).- A solution of 1,1-dimethoxy-3-nitro-3-methylbutan-2-ol (**2b**) (8.69 g, 45 mmol), ethylen glycol (6.7 mL, 120 mmol) and *p*-toluensulfonic acid (885 mg, 4.5 mmol) in anhydrous benzene (150 mL) was heated to reflux into a Soxhlet apparatus containing 3Å molecular sieves (80 g). After 3 h, a solution of potassium bicarbonate was added and the reaction mixture was extracted with ether (3 x 40 mL), washed with brine and saturated sodium bicarbonate, dried ($MgSO_4$) and rotoevaporated to obtain a colorless oil (6.8 g, 80% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.98 (1 H, d, *J* = 3.7 Hz), 4.17 (1 H, dd, *J* = 5.6, 3.7 Hz), 4.08-3.87 (4 H, m), 2.61 (1 H, d, *J* = 5.6 Hz), 1.65 (3 H, s), 1.62 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 101.96, 89.56, 75.13, 65.41, 65.37, 23.06, 21.38.

1-(4,5-Diphenyl-1,3-dioxolan-2-yl)-3-nitro-3-methylbutan-2-ol (7).- A solution of 1,1-dimethoxy-3-nitro-3-methylbutan-2-ol (**2b**) (1.93 g, 10 mmol), racemic hydrobenzoin (2.41 g, 10 mmol) and *p*-toluensolfonic acid (190 mg, 1 mmol) in dichloromethane (25 mL) was refluxed into a Soxhlet apparatus charged with 3Å molecular sieves (15 g). After 86 h, the reaction mixture was treated with a solution of potassium bicarbonate, extracted with dichloromethane (3 x 10 mL), washed with brine and saturated $NaHCO_3$, dried (Na_2SO_4) and rotoevaporated to obtain a colorless solid: 2.23 g (65% yield). ^{1}H NMR (200 MHz, $CDCl_3$): Major isomer δ 7.42-7.22 (10 H, m), 5.56 (1 H, d, *J* = 3.7 Hz), 4.88 (1 H, d, *J* = 8.2 Hz), 4.83 (1 H, d, *J* = 8.2 Hz), 4.50 (1 H, dd, *J* = 5.2, 3.7 Hz), 2.98 (1 H, d, *J* = 5.2 Hz), 1.79 (3 H, s), 1.75 (3 H, s). Minor isomer δ 7.42-7.22 (10 H, m), 5.52 (1 H, d, *J* = 3.9 Hz), 4.88 (1 H, d, *J* = 8.2 Hz), 4.83 (1 H, d, *J*

= 8.2 Hz), 4.46 (1 H, dd, J = 5.2, 3.9Hz), 2.96 (1 H, d, J = 5.2 Hz), 1.77 (3 H, s), 1.76 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ (aliphatic carbons only) 102.87, 102.79, 89.77, 89.64, 86.90, 86.77, 85.21, 85.09, 75.88, 75.80, 23.42, 22.61, 21.30, 21.26.

1,1-Dimethoxy-3-amino-3-methylbutan-2-ol (3b).- Into a 250 mL round bottomed flask are added in the sequence: 500 mg of 10% Pd/C (Fluka reagent), 100 mL of THF, 100 mL of MeOH, 3.5 g of ammonium formate (55 mmol) and 2.0 g of 1,1-dimethoxy-3-nitro-3-methylbutan-2-ol (10 mmol). (CAUTION! A different sequence of addition of the reagents led the mixture to ignite spontaneously!). The reaction mixture was stirred at room temperature up to complete consumption of the nitro compound (ca. 5 h, NMR monitorng), diluted with ether (200 mL), filtered and rotoevaporated to obtain a yellow oil. Vacuum distillation (75°, 0.1 torr) delivers 1.3 g (80% yield) of a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.41 (1 H, d, J = 5.3 Hz), 3.71 (1 H, d, J = 5.3 Hz), 3.46 (3 H, s), 3.43 (3 H, s), 2.40-1.90 (3 H, bs), 1.15 (3 H, s), 1.09 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 104.54, 76.16, 54.62, 54.44, 51.76, 27.95, 26.26.

6-Carboxy-3,3,5,5-tetramethylmorpholinone Dimethylacetal (4b).- Solid NaOH (8.0 g, 200 mmol) was added during 7 h to a cooled (0°) solution of acetone (29.37 mL, 400 mmol), chloroform (4.8 mL, 60 mmol), 1,1-dimethoxy-3-amino-3-methylbutan-2-ol (6.5 g, 40 mmol). The reaction mixture was slowly allowed to reach room temperature overnight and filtered. The colorless solid displays the following data: ^{1}H NMR (200 MHz, D_2O): δ 4.38 (1 H, d, J = 4.46 Hz), 3.36 (3 H, s), 3.33 (3 H, s), 3.29 (1 H, d, J = 4.46 Hz), 2.40-1.90 (2 H, bs), 1.20 (6 H, s), 1.11 (3 H, s), 1.04 (3 H, s). ^{13}C NMR (50 MHz, D_2O): δ 120.99, 104.78, 75.58, 60.44, 58.56, 55.64, 55.59, 28.35, 27.35, 23.42. IR (KBr) ν_{max}: 1569.3. It was treated with conc. HCl up to pH 3 and refluxed. After 2 h most water was removed by rotoevaporation, toluene was added (ca. 10 mL) and again rotoevaporated to removed azeotropically the residual water. Et_3N was added and the reaction mixture heated at reflux for 1.5 h, cooled and filtered. After rotoevaporation, a colorless oil was obtained: 2.31 g, 50% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.44 (1 H, d, J = 4.45 Hz), 4.20 (1 H, d, J = 4.45 Hz), 3.48 (3 H, s), 3.45 (3 H, s), 1.85 (1 H, bs), 1.44 (3 H, s), 1.42 (3 H, s), 1.28 (3 H, s), 1.17 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.64, 103.94, 85.76, 55.45, 55.40, 54.17, 50.23, 30.85, 30.15, 28.06, 24.12.

Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.39; H, 8.89; N, 5.81

3-Methyl-2-en-2-ol-butanal (9).- The solid product obtained by filtration in the preparation of **4b** (1 g) was dissolved in water (20 mL) and brought to pH 3 with conc. HCl. The solution was refluxed for 4 h, during which time colorless needles form within the reflux condenser. The highly volatile crystals are collected and analyzed. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.78 (1 H, s), 5.90 (1 H, s), 2.09 (3 H, s), 1.96 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 183.25, 145.25, 131.22, 19.08, 16.43. MS (70 eV): *m/z* 100, 84, 72, 57, 53.

***N*-(4-Hydroxy-5-methyl-hex-1-en-5-yl)carbamic Acid *t*-Butyl Ester (12)**.- A solution of aldheyde **11** (3.74 g, 20 mmol) in 20 mL dichloromethane, cooled at -78°, was added dropwise to a 22 mL, 1 M solution of $TiCl_4$ in dichloromethane. After 10 min, trimethylsilylpropene (3.5 mL,

22 mmol) was added dropwise at -78° and the reaction mixture was stirred at room temperature for 1 h. After addition of water (10 mL) the mixture was extracted with dichloromethane (3 x 25 mL). The aqueous phase was neutralized with $NaHCO_3$ and extracted with ether. The ether and dichloromethane solution are combined, dried ($MgSO_4$) and evaporated to obtain an oil (1.36 g, 30% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.10-5.80 (1 H, m), 5.20-5.05 (2 H, m), 4.68 (1 H, bs), 3.88 (1 H, bs), 3.60-3.50 (1 H, m), 3.40-1.95 (2 H, m), 1.43 (9 H, s), 1.36 (3 H, s), 1.22 (6 H, s).

6-(1-Propene-3-yl)-3,3,5,5-tetramethylmorpholinone (4c).- Solid NaOH (1.0 g, 25 mmol) was slowly added during 7 h to a cooled (0°) solution of acetone (2.44 mL, 50 mmol), chloroform (0.6 mL, 7 mmol), *N*-(4-hydroxy-5-methyl-hex-1-en-5-yl)-carbamic acid *t*-butyl ester **12** (1.14 g, 5 mmol). The reaction mixture was slowly let to reach room temperature overnight and filtered. The colorless solid was treated with HCl up to pH 3 and heated to reflux. After 4 h at reflux, most of the water was taken off at the rotoevaporator, toluene added (ca. 10 mL) and again evaporated on a rotary evaporator to remove all the water azeotropically. Triethylamine (1.4 mL, 10 mmol) was added and the solution refluxed for 2 h in 20 mL of toluene, cooled, filtered and evaporated *in vacuo* to obtain a colorless oily residue (0.4 g, 40% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.05-5.70 (1 H, m), 5.20-4.90 (2 H, m), 4.22 (1 H, d, J = 6.4 Hz), 4.17 (1 H, s), 2.30 (2 H, d, J = 6.4 Hz), 1.44 (3 H, s), 1.43 (3 H, s), 1.14 (3 H, s), 1.12 (3 H, s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 175.21, 133.81, 117.77, 87.83, 54.69, 51.75, 45.34, 31.23, 30.64, 27.26, 21.35.
Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 67.25; H, 9.39; N, 6.90

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