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A CONVENIENT SYNTHESIS OF DIVERSELY SUBSTITUTED N,N-DIMETHYL-4-OXO-2-(*E*)-ALKENAMIDES

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***Abstract**: An efficient synthesis of diversely substituted N,N-dimethyl-4-oxo-2-(E)-alkenamides is reported. These derivatives were obtained in three steps from 1,4-benzodioxin with fair to good yields.*

In recent years, there has been widespread interest regarding the synthesis of 4-oxo-2-(*E*)-alkenoates, a familly of structural fragments which populates a variety of biologically important natural products such as macrolide antibiotics[1,2]. In addition, these structures can be used as nucleophiles acceptors[3] or as potent dienophiles in Diels-Alder reactions[4]. Although a number of methods exist for the preparation of these structural units, there are many restrictions concerning the

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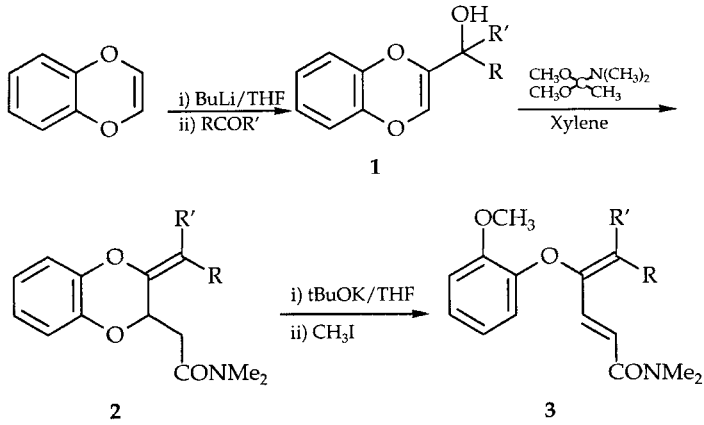
substituents, the mildness of the reaction conditions as well as the simplicity and the availability of starting materials[5].

The convenient preparation of N,N-dimethyl-4-oxo-2-(*E*)-alkenamides is reported. In general, the synthesis of these compounds is not described as well as the preparation of the corresponding esters.

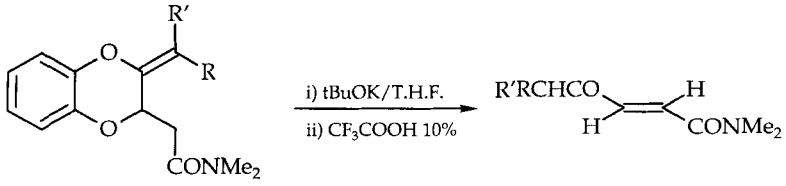
As part of further studies on the chemistry of 1,4-benzodioxin and its synthetic applications, the synthesis of 1,3-dienes **3** bearing both electron-donor and acceptor substituents in fair to good yields has been recently reported[6,7] (Scheme 1), as well as their use in organic synthesis[8]. The key step of this general method is the access to the unknown alkylidene-2,3-dihydro-1,4-benzodioxins **2** via an Eschenmoser transposition[9].



Scheme 1

These derivatives were thought to constitute versatile intermediates in the preparation of N,N-dimethyl-4-oxo-2-(*E*)-alkenamides **4**. Indeed, when compounds **2** were submitted to a basic elimination reaction immediately followed by acidic hydrolysis with a 10% aqueous solution of trifluoroacetic acid

(instead of adding CH_3I for the synthesis of the dienes **3**), the corresponding expected N,N-dimethyl-4-oxo-2-(*E*)-alkenamides **4** were obtained in high yields (Scheme 2, Table 1). The stereochemistry of compounds **4** is well-defined and determined by ^{1}H-NMR; the basic elimination step leads to the stereoisomer *E* only. No trace of stereoisomer *Z* was detected.



2 **4**

Scheme 2

In conclusion, a simple and rapid way to synthetize stereochemically well-known N,N-dimethyl-4-oxo-2-(*E*)-alkenamides **4** from readily available starting materials has been developed.

Experimental Section

Melting points are uncorrected and were determined in capillary tubes with a Büchi apparatus. I.R. spectra were recorded using a Perkin-Elmer 297 spectrometer. Mass spectra were recorded using a Nermag R-10-10-C apparatus. ^{1}H NMR spectra were recorded using a Bruker AM-300 WB (300 MHz) spectrometer. Chemical shifts were reported in ppm units with TMS as the internal standard. Coupling constants were reported in hertz. Thin layer

Table 1

Compounds	R	R'	Yields
4a	H	H	99%
4b	H	CH_3	81%
4c	H	C_3H_7	85%
4d	H	C_7H_{15}	86%
4e	CH_3	CH_3	82%
4f	-$(CH_2)_5$-		76%

chromatographies were performed using Kieselgel Merck 60 F_{254} and the preparative silica columns were performed on Merck 60 (70-230 mesh) silica gel.

Preparation of N,N-dimethyl-4-oxo-2-(*E*)-alkenamides 4. General Procedure:

A solution of the alkylidene-2,3-dihydro-1,4-benzodioxanes **2** (1 mmol) in dry T.H.F. (5 ml) was treated with *t*-BuOK (135 mg, 1.2 mmol) in an atmosphere of argon, at 0°C for 1 h.

After adding of a 10% aqueous solution of trifluoroacetic acid (until pH=1), the mixture was stirred at reflux for 24 h for compounds **3a-d** and for 48 h for products **3e** and **3f**.

After extracting of the solution with ether, the organic phase was dried and concentrated under reduced pressure. The residue was purified by

chromatography on silica gel ($MeOH/CH_2Cl_2$: 1/99) to give N,N-dimethyl-4-oxo-2-(*E*)-alkenamides **4** in good yields (76-99%).

4a: white solid; F=66°C; 140 mg; yield=99%; I.R. (KBr): 1695 (CO ketone), 1640 (CO amide), 1610 cm^{-1} (C=C); ^1H N.M.R. ($CDCl_3$): 2.30 (s, 3H, CH_3CO), 3.0 and 3.09 (2s, 6H, $N(CH_3)_2$), 6.98 (d, 1H, J=14.3, $\underline{CH}COCH_3$), 7.17 (d, 1H, J=14.3, $\underline{CH}CON(CH_3)_2$); M.S. ($NH_3$): m/z=142 (M+1); Anal. calcd. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.68; H, 7.89; N, 10.01 %.

4b: yellow solid; F=49°C; 126 mg; yield=81%; I.R. (KBr): 1695 (CO ketone), 1640 (CO amide), 1610 cm^{-1} (C=C) ; ^1H N.M.R. ($CDCl_3$): 1.10 (t, 3H, J=7.2, CH_3), 2,63 (q, 2H, J=7.2, CH_2), 3.03 and 3.11 (2s, 6H, $N(CH_3)_2$), 7.06 (d, 1H, J=15.4, $\underline{CH}COCH_2$), 7.24 (d, 1H, J=15.4, $\underline{CH}CON(CH_3)_2$); M.S. ($NH_3$): m/z=156 (M+1); Anal. calcd. for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.98; H, 8.49; N, 9.07 %.

4c: brown oil; 156 mg; yield=85%; I.R. (neat): 1690 (CO ketone), 1640 (CO amide), 1615 cm-1 (C=C) ; 1H N.M.R. ($CDCl_3$): 0.91 (t, 3H, J=6.1, CH_3), 1.27 to 1.43 (m, 2H, $\underline{CH_2}CH_3$), 1.57 to 1.70 (m, 2H, $\underline{CH_2}CH_2CO$), 2.61 (t, 2H, J=6.1, CH_2CO), 3.04 and 3.12 (2s, 6H, $N(CH_3)_2$), 7.07 (d, 1H, J=15.5, $\underline{CH}CO(CH_3)_2$), 7.24 (d, 1H, J=15.5, $\underline{CH}CON(CH_3)_2$); M.S. ($NH_3$): m/z=184 (M+1); Anal. calcd. for $C_{10}H_{17}NO_2$: C, 65.56; H, 9.35; N, 7.64. Found: C, 65.62; H, 9.39; N, 7.69%.

4d: yellow solid; F=44°C; 206 mg; yield=86%; I.R. (KBr): 1690 (CO ketone), 1640 (CO amide), 1615 cm^{-1} (C=C); ^1H N.M.R. ($CDCl_3$): 0.85 to 0.92 (m, 3H, CH_3), 1.18 to 1.39 and 1.57 to 1.74 (2m, 12H, $(CH_2)_6$), 2.60 (t, 2H, J=7.1,

CH_2CO), 3.05 and 3.13 (2s, 6H, $N(CH_3)_2$), 7.08 (d, 1H, J=15.0, $\underline{CH}CO(CH_2)_7$), 7.24 (d, 1H, J=15.0, $\underline{CH}CON(CH_3)_2$); M.S. ($NH_3$): m/z=240 (M+1); Anal. calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.31; H, 10.62; N, 5.86%.

4e: brown oil; 139 mg; yield=82%; I.R. (neat): 1690 (CO ketone), 1640 (CO amide), 1620 cm^{-1} (C=C); ^1H N.M.R. ($CDCl_3$): 1.13 (d, 6H, J=5.5, $(CH_3)_2$), 2.77 to 2.83 (m, *1H, CHCO*), 3.02 and 3.10 (2s, *6H*, $N(CH_3)_2$), 7.16 (d, *1H*, *J*=15.3, $\underline{CH}COCH(CH_3)_2$), 7.26 (d, 1H, J=15.3, $\underline{CH}CON(CH_3)_2$); M.S. ($NH_3$): m/z=170 (M+1); Anal. calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.91; H, 8.99; N, 8.33%.

4f: yellow solid; F=61°C; 159 mg; yield=76%; I.R. (KBr): 1690 (CO ketone), 1640 (CO amide), 1620 cm^{-1} (C=C) ; ^1H N.M.R. ($CDCl_3$): 1.17 to 1.44 and 1.63 to 1.96 (m, 10H, cyclohexyl), 2.46 to 2.58 (m, 1H, CHCO), 3.04 and 3.13 (2s, 6H, $N(CH_3)_2$), 7.20 (d, 1H, J=15.5, $\underline{CH}$=CHCON$(CH_3)_2$), 7.28 (d, 1H, J=15.5, $\underline{CH}CON(CH_3)_2$); M.S. ($NH_3$): m/z=210 (M+1); Anal. calcd. for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.97; H, 9.24; N, 6.80%.

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