A Simple, Efficient, Two-Step Synthesis of Symmetric 2,7-Dialkyl-1,6-Dioxaspiro[4.4]nonanes

Roberto Ballini*, Giovanna Bosica and Alessandra Uselli

Dipartimento di Scienze Chimiche dell'Università,
62032 Camerino, Italy

Received June 28, 1993

A two-step synthesis of symmetric 2,7-dialkyl-1,6-dioxaspiro[4.4]nonanes has been achieved by double Michael addition of nitromethane with two moles of enones on Amberlyst A21, followed by *in situ* reduction with sodium borohydride, then spontaneous spiroketalization of the obtained nitrodiol, by the Nef reaction under acidic conditions, affords the title compounds in good yields.

J. Heterocyclic Chem., **31**, 259 (1994).

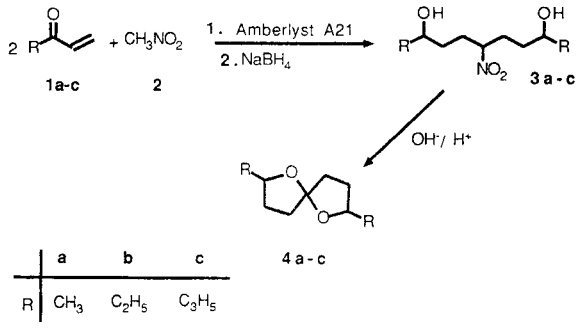
Spiroketals [1-4] enjoy widespread occurrence as structures of naturally occurring substances from many sources, including insects, microbes, plants, fungi, and marine organisms. The increasing pharmacological importance of compounds containing spiroketal assembles has triggered intense interest in both their synthesis and chemicals reactivity.

One of the widely accepted procedures, to synthesize these spiroketals involves intramolecular cyclization of suitably placed dihydroxyketones which, generally, can be obtained using organometallic species [5].

During our program directed towards the total synthesis of insect pheromones incorporating the spiroketal substructure, we have reported [6] that mono-alkylated spiroketals can be easily and conveniently prepared from functionalized nitroalkanes, without the problems associated with the use of organometallic species.

In this paper we report a simple, two-step, inexpensive, large scale method to obtain 2,7-dialkyl-1,6-dioxaspiro[4.4]-nonanes, important pheromone components [7-12], in which the starting point (Scheme 1) is the double 1,4-addition of nitromethane **2** with two moles of enone **1**, on Amberlyst A21, without solvent, and then, after washing the Amberlyst with acetonitrile/water and direct reduction by addition of sodium borohydride, the nitro-diol **3** was obtained, one-pot, in good yields (60-80%).

Scheme 1



The transformation of the carbon bearing the nitro group into a carbonyl group has been efficiently achieved by conversion of the nitro group, under basic condition (sodium hydroxide), into the corresponding nitronate which by acidification in two-layer (sulfuric acid/pentane) gave, by spontaneous spiroketalization, the compound **4** (71-80% yields).

By this method 2,7-dimethyl-1,6-dioxaspiro[4.4]nonane **4a** has been prepared in 50% overall yield, 2,7-diethyl-1,6-dioxaspiro[4.4]nonane **4b**, isolated [8] from *Andrena Wilkella, Andrena Ocreata,* and *Andrena Ovatula,* has been obtained in 42% overall yield, while 2,7-dipropyl-1,6-dioxaspiro[4.4]nonane **4c**, isolated [9] from *Andrena Haemorroa,* has been prepared in 64% overall yield.

In conclusion we think that the reported, two-step, method to afford the title compounds presents important advantages such as mild reaction conditions, good yields, use of cheap commercial available reactants, simple workup, and large scale application.

EXPERIMENTAL

All ^1H nmr and ^{13}C nmr were recorded, with tetramethylsilane as the internal standard and in chloroform-d as the solvent, at 200 and 50 MHz respectively on a Varian Gemini 200. Mass spectra (gc-ms) were recorded with a HP G1300A work station formed by a HP 5890 GC equipped with a methylsilicone capillary column and a HP 5971 mass detector. All of the products **4** were monitored by gc, performed on a Carlo Erba Fractovap 4160 using a capillary column of Duran glass (0.32 mm x 25 m), stationary phase OV1 (film thickness 0.4-0.45 nm). Microanalyses were performed by using a C, H, N Analyzer Model 185 from Hewlett-Packard Co. Nitromethane **2**, 1-buten-3-one **1a**, and 1-penten-3-one **1b** were purchased from Aldrich; 1-hexen-3-one **1c** was purchased from Heraeus.

General Procedure for the Synthesis of Nitrodiols **3**.

Nitromethane **2** (2.44 g, 0.04 mole) and enone **1** (0.08 mole) were mixed by cooling with an ice/bath. After stirring for 10 minutes, Amberlyst A21 (12 g) was added and stirring was continued for 8 hours at room temperature, before being extracted with acetonitrile (3 x 30 ml). To the filtered extract water (130 ml) was added, then, after cooling at 0°, sodium borohydride (6.08 g, 0.16 mole) was added during 30 minutes. Stirring was continued for 90 minutes and then the solution was acidified (2*N* hydrochloric acid), extracted with diethyl ether, dried (sodium sulfate) and

evaporated to obtain the crude **3** which it is pure enough for the next step, or, alternatively, can be purified by flash chromatography (cyclohexane-ethyl acetate-ethanol = 3.5:6:0.5, as the eluent).

5-Nitro-2,8-nonanediol (**3a**).

The compound was obtained as a yellow oil in 70% yield; ir (potassium bromide): ν max 3360 (OH), 1545 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.18 (d, J = 7.4 Hz, 6 H), 1.32-1.52 (m, 4 H), 1.8-2.2 (m, 4 H), 3.7-3.9 (m, 2 H), 4.45-4.62 (m, 1 H).

Anal. Calcd. for $C_9H_{19}NO_4$: C, 52.67; H, 9.33; N, 6.82. Found: C, 52.88; H, 9.10; N, 7.00.

6-Nitro-3,9-undecanediol (**3b**).

This compound was obtained as a yellow oil in 60% yield; ir (potassium bromide): ν max 3360 (OH), 1545 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.93 (t, J = 7.5 Hz, 6 H), 1.3-1.6 (m, 8 H), 1.8-2.2 (m, 4 H), 3.45-3.63 (m, 2 H), 4.48-4.68 (m, 1 H).

Anal. Calcd. for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. Found: C, 56.78; H, 10.02; N, 6.14.

7-Nitro-4,10-tridecanediol (**3c**).

This compound was obtained as a yellow oil in 80% yield; ir (potassium bromide): ν max 3270 (OH), 1540 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.9 (t, J = 6.8 Hz, 6 H), 1.2-1.7 (m, 12 H), 1.8-2.2 (m, 4 H), 3.53-3.72 (m, 2 H), 4.45-4.68 (m, 1 H).

Anal. Calcd. for $C_{13}H_{27}NO_4$: C, 59.74; H, 10.41; N, 5.36. Found: C, 59.88; H, 10.58; N, 5.18.

General Procedure for the Synthesis of 1,7-Dialkyl-1,6-dioxaspiro-[4.4]nonane (**4**).

A solution of nitrodiol **3** (20.4 mmoles) in absolute ethanol (45 ml) was added dropwise to a solution of sodium hydroxide (3.3 g, 81 mmoles) in ethanol (45 ml) under nitrogen at room temperature. The mixture was stirred for 10 minutes and then the solvent was evaporated. A solution of the resulting salt in water (90 ml) was slowly added to a two-layer mixture of sulfuric acid (10 ml of concentrated sulfuric acid in 100 ml of water) and *n*-pentane (90 ml) with stirring under ice-water bath cooling. Stirring was continued for 1 hour at 0° and the pentane layer separated. The aqueous layer was then extracted with pentane. The organic solutions were combined, dried and distilled to afford the pure **4**.

2,7-Dimethyl-1,6-dioxaspiro[4.4]nonane (**4a**).

This compound was obtained as a colorless liquid in 71% yield (*E,Z/E,E/E,Z* = 48:35:17%), bp 135°/65 mm Hg (Kugelrohr); ^1H nmr (deuteriochloroform): δ 1.98 (d, J = 6.19 Hz, 6 H, *E,E*), 1.21 (d, J = 6.14 Hz, 3 H, *E*), 1.29 (d, J = 6.17 Hz, 3 H, *Z*), 1.30 (d, J = 6.14 Hz, 6 H, *Z,Z*), 1.85-2.4 (m, 8 H), 4.05-4.3 (m, 2 H); ms: m/z 156 (M^+), 141, 112, 101 (base peak), 85, 55.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.00; H, 10.49.

2,7-Diethyl-1,6-dioxaspiro[4.4]nonane (**4b**).

This compound was obtained as a colorless liquid in 71% yield (*E,E/E,Z* = 50:50%), bp 115°/4 (mm Hg (Kugelrohr); ^1H nmr (deuteriochloroform): δ 0.89 (t, J = 7.5 Hz, 6 H, *E,E*), 0.902 (t, J = 7.4 Hz, 3 H, *E*), 0.908 (t, J = 7.4 Hz, 3 H, *Z*), 1.4-2.15 (m, 12 H), 3.85-4.05 (m, 2 H); ms: m/z 184 (M^+), 155 (base peak), 126, 97, 85, 69.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.7; H, 10.94. Found: C, 71.48; H, 11.08.

2,7-Dipropyl-1,6-dioxaspiro[4.4]nonane (**4c**).

This compound was obtained as a colorless liquid in 80% yield (*E,Z/E,E/Z,Z* = 48:33:19%), bp 150°/6 mm Hg (Kugelrohr); ^1H nmr (deuteriochloroform): δ 0.91 (t, J = 7.1 Hz, 6 H), 1.2-2.2 (m, 16 H), 3.9-4.15 (m, 12 H); ^{13}C nmr (deuteriochloroform): δ 14.6, 19.5, 19.6, 19.8, 30.5, 30.7, 31.2, 35.3, 35.9, 36.5, 36.7, 38.4, 40.1, 40.3, 78.0 (*E* -CH), 78.3 (*E* -CH), 80.1 (*Z* -CH), 80.2 (*Z* -CH), 114.4 (*Z,Z*), 114.6 (*E,Z*), 114.8 (*E,E*); ms: m/z 212 (M^+), 170, 169 (base peak), 140, 129 (26), 111, 85, 83, 69, 55.

Anal. Calcd. for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.7; H, 11.5.

Acknowledgments.

We thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST)-Italia for financial support.

REFERENCES AND NOTES

[1] F. Perron and K. F. Albizati, *Chem. Rev.*, **89**, 1617 (1989).

[2] A. F. Kluge, *Heterocycles*, **24**, 1699 (1986).

[3] T. L. Boivin, *Tetrahedron*, **43**, 3309 (1987).

[4] K. Mori, *Tetrahedron*, **45**, 3233 (1989).

[5] J. S. Yadav and V. R. Gadgil, *Tetrahedron Letters*, **31**, 6217 (1990) and references cited therein.

[6] R. Ballini and M. Petrini, *J. Chem. Soc., Perkin Trans. 1*, 3159 (1992).

[7] W. Francke and W. Reith, *Liebigs Ann. Chem.*, 1 (1979).

[8] W. Francke and W. Reith, *Z. Naturwiss.*, **67**, 149 (1980).

[9] W. Francke and W. Reith, *Z. Naturforsch.*, **36c**, 928 (1981).

[10] G. Bergstrom, W. Tengo, W. Reith and W. Francke, *Z. Naturforsch.*, **37c**, 1124 (1982).

[11] M. V. Perkins, W. Kitching, R. A. I. Drew, C. J. Moore and W. A. Konig, *J. Chem. Soc., Perkin Trans. 1*, 1111 (1990).

[12] D. Enders, W. Dahmer, E. Dederichs, W. Gatzweiler and P. Weuster, *Synthesis*, 1013 (1990).