Regiochemistry of the Reaction of 2-Acylcyclohexanones with Trimethyl Orthoformate: A Convenient One-Pot Method to Obtain 7,7-Dimethoxy Alkanoate Methyl Esters

Marcos A. P. Martins,* Giovani P. Bastos, Adilson P. Sinhorin, Alex F. C. Flores, Helio G. Bonacorso, Nilo Zanatta

Departamento de Química, Universidade Federal de Santa Maria, 97.105-900 Santa Maria, RS, Brazil
Fax +55 55 2208031; E-mail: mmartins@base.ufsm.br http://www.ufsm.br/nuquimhe

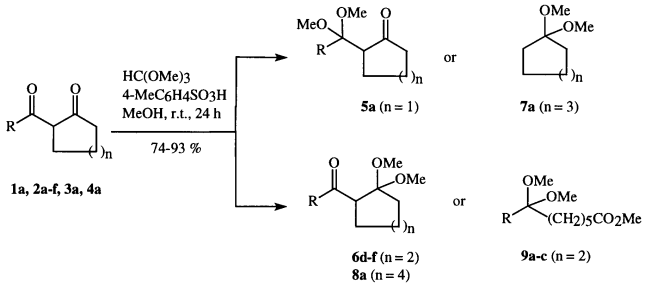
Received 14 March 1999

Abstract: The regiochemistry of the reaction of 2-acylcyclohexanones [containing 2-acyl groups, C(O)R, where R = Me, Et, CH_2Ph, CF_3, Ph and OMe] with trimethyl orthoformate to obtain the corresponding acetal derivative is reported. Compounds with R = alkyl groups showed to be convenient synthons for a one-pot method to obtain 7,7-dimethoxy alkanoate methyl esters under mild conditions. The results of the reaction of 2-acetylcyclopentanone, -heptanone and -octanone with trimethyl orthoformate are also reported.

Key words: acetals, β-diketones, 2-acylcycloalkanones, trimethyl orthoformate, reverse claisen condensation

β-Alkoxyvinyl halomethyl ketones or -diketone derivatives are used by our research group as precursors for the synthesis of 5-, 6- and 7-membered heterocycles.[1,2] These precursors have been synthesized by the haloacetylation of enol ethers.[3-5] As a part of our research program, we developed the synthesis of -alkoxyvinyl trihalomethyl ketones or -diketone derivatives from the trihaloacetylation of enol ethers generated *in situ*[4,5] from the respective acetals, as an alternative one-pot procedure with great advantages over the direct acylation of enol ethers. However, during the preparation of the 2-acetyl cyclohexanone dimethyl acetal, cleavage of the cyclohexanone ring affording 7,7-dimethoxyoctanoate methyl ester was observed. Although cleavage of the cyclohexanone ring (*reverse Claisen condensation*) was observed by several authors[6] (*e.g.*, the synthesis of 7-oxoalkanoic acid derivatives from the reaction of acylcyclohexanones with sodium hydroxide), we have not found reported in the literature the *reverse Claisen condensation* under mild conditions and in a one-pot procedure to obtain 7-oxoalkanoate ester acetal derivatives. The aim of this work is to determine the effect of the acyl group on the regiochemistry of the acetalization and the optimization of the reaction conditions to obtain 7,7-dimethoxy alkanoate methyl esters. The reaction of 2-acetylcyclopentanone, -heptanone and -octanone with trimethyl orthoformate was also studied (Scheme).

2-Acyl cycloalkanones **1a-f**, **2a**, **3a**, **4a** were synthesized from the reaction of the cycloalkanone enamine derivative with the respective acyl halide or anhydride as reported by Stork *et al.* .[7] The reaction of **1-4** with trimethyl orthoformate and *p*-toluenesulfonic acid in methanol as solvent was carried out in a molar ratio 1:1.5:0.01, respectively. The reaction mixture was kept for 24 hours at room temperature (25-30 °C), after which time it was neutralized with dry sodium carbonate and the products **5-9** were purified by distillation (Table).



Compound	a	b	c	d	e	f
R	Me	Et	CH_2Ph	CF_3	Ph	OMe

Compound	1,5	2,6	3,7	4,8
n	1	2	3	4

Scheme

In the case of cyclohexanone derivatives **2a-f**, the regiochemistry of the reaction was governed by the electronic substituent effect of R. When R is Me, Et or CH_2Ph, the cleavage of the cyclohexanone ring (C1-C2 bond) was observed and 7,7-dimethoxyalkanoate methyl esters **9a-c** were obtained. On the other hand, when R is Ph, CF_3 or OMe, 2-acyl cyclohexanone dimethyl acetals **6d-f** were obtained. These results suggest that RC(O) groups with a large electron withdrawing effect led to the cleavage of the cyclohexanone ring and the RC(O) groups with an attenuated electron withdrawing effect led to the cyclohexanone dimethyl acetals.

The reaction of cyclopentanone **1a** with trimethyl orthoformate leads to the isolation of acetal **5a**, and the cycloheptanone **3a** led to the acetal **7a** by cleavage of C2-COMe bond. The reaction of cyclooctanone derivative **4a** leads to the isolation of acetal **8a**, similar to products **6d-f** obtained from cyclohexanone derivatives **2d-f**. Thus, while 2-acetylcyclohexanone **2a** and 2-acetylcycloheptanone **3a** react with trimethyl orthoformate to give the *reverse Claisen products* **9a** (with cleavage of C1-C2 bond) and **7a** (with cleavage of C2-COMe bond), respectively; the reaction of 2-acetylcyclopentanone **1a** and 2-acetylcy-

Table. Selected[8] physical and NMR data of **5a**, **7a, 6d-f**, **8a**, **9a-c**.

Product	Yield (%)	Bp (°C)/ mBar	^{1}H NMR δ	^{13}C NMR δ
5a	75	74/2	2.44 (H2), 1.53-2.20 -$(CH_2)_3$-, 3.11, 3.16 (OMe1), 1.20 (H7)	215.8 (C1), 53.9 (C2), 18.5 (C3), 26.7 (C4), 40.0 (C5), 102.6 (C6), 20.6 (C7), 48.1, 48.6 (OMe1)
6d	82	75/25	3.50 (H2), 1.35 - 2.0 -$(CH_2)_4$-, 3.08, 3.15 (OMe1)	100.2 (C1), 44.7 (C2), 25.2 (C3), 19.9 (C4), 21.8 (C5), 29.1 (C6), 191.1 (C7), 115.4 (C8), 47.7, 47.3 (OMe1)
6e	85	137/2	4.02 (H2), 1.3 - 2.4 -$(CH_2)_4$-, 3.07, 3.23 (OMe1), 7.51, 7.95 (Ph)	100.8 (C1), 45.3 (C2), 24.5 (C3), 20.3 (C4), 22.0 (C5), 28.6 (C6), 199.4 (C7), 137.3, 132.4, 128.4, 127.9 (Ph), 47.6, 46.8 (OMe1)
6f	80	85/25	2.9 (H2), 1.4 - 2.0 -$(CH_2)_4$-, 3.17, 3.21 (OMe1), 3.7 (OMe7)	99.9 (C1), 45.5 (C2), 26.0 (C3), 20.6 (C4), 21.8 (C5), 28.4 (C6), 173.1 (C7), 47.7, 47.3 (OMe1), 51.4 (OMe8)
7a	74	65-66/2	1.18 - 2.10 -$(CH_2)_6$-, 3.09, 3.21 (OMe1)	104.3 (C1), 36.4 (C2, C7), 21.0 (C3, C6), 29.0 (C4, C5) 47.0, 47.4 (OMe1)
8a	86	88-90/2	2.38 (H2), 1.29 - 1.88 -$(CH_2)_6$-, 3.15, 3.18 (OMe1), 1.38 (H10)	102.8 (C1), 52.5 (C2), 24.4 (C3), 27.9 (C4), 29.2 (C5), 30.0 (C6), 25.1 (C7), 208.3 (C9), 18.0 (C10), 47.5, 48.3 (OMe1)
9a	82	90/2	1.21 (H8), 1.29 (H4), 1.50-1.70 (H3, H5, H6), 2.27 (H2), 3.12 (Ome7), 3.62 (OMe1)	172.2 (C1), 36.7 (C2), 25.3 (C3), 21.32 (C4), 24.3 (C5), 34.4 (C6), 102.0 (C7), 29.8 (C8), 51.8 (OMe1), 48.4 (OMe7)
9b	93	110/25	2.32 (H2), 1.50 - 1.64 (H3, H5, H6), 1.27 (H4), 2.34 (H8), 0.82 (H9)	173.9 (C1), 33.9 (C2), 28.1 (C3), 24.1 (C4), 24.8 (C5), 28.4 (C6), 101.8 (C7), 60.4 (C8), 51.1 (OMe1), 47.3 (OMe7)
9c	80	160/25	1.40 - 2.1 -$(CH_2)_5$-, 3.17, 3.22 (OMe7), 3.7 (OMe1), 7.2 -7.3 (Ph)	169.4 (C1), 33.6 (C2), 28.9 (C3), 23.7 (C4), 25.7 (C5), 32.2 (C6), 102.1 (C7), 66.3 (C8), 51.1 (OMe1), 46.2 (OMe7), 126.8, 127.6, 128.3, 136.7 (Ph)

clooctanone **4a** react with trimethyl orthoformate to give acetals **5a** and **8a**, respectively, with no C-C bond cleavage.

Selected physical and spectral data of **5a**, **6d-f**, **7a**, **8a**, **9a-c** are presented in the Table.[8]

Synthesis of 7,7-Dimethoxyalkanoate Methyl Esters 9a-c and Cycloalkanone Derivatives 5a, 6d-f, 7a, 8a; General Procedure:

Trimethyl orthoformate (16.4 mL, 150 mmol) and p-toluenesulfonic acid (0.15g, 0.78 mmol) in dry methanol (30 mL) were added to an Erlenmeyer flask (250 mL) with 2-acyl cycloalkanone **1-4** (100 mmol) and the mixture was kept for 24 hours at room temperature (25-30 °C). The mixture was neutralized with sodium carbonate and filtered. The solvent was removed in vacuo and products **5a**, **6d-f**, **7a**, **8a**, **9a-c** were purified by distillation, (see Table).

Acknowledgement

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq / PADCT), Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS) for financial support. The fellowships from CNPq, CAPES and FAPERGS are also acknowledged.

References and Notes

(1) Martins, M.A.P.; Zoch, A.N.; Bonacorso, H.G.; Zanatta, N.; Clar, G. *J. Heterocycl. Chem.* **1995**, *32*, 739.
Martins, M.A.P.; Flores, A.F.C.; Freitag, R.A.; Zanatta, N. *J. Heterocycl. Chem.* **1995**, *32*, 731.
Martins, M.A.P.; Flores, A.F.C.; Freitag, R.A.; Zanatta, N. *J. Heterocycl. Chem.* **1996**, *33*, 1223.
Martins, M.A.P.; Siqueira, G.M.; Bastos, G. P.; Zanatta, N. *J. Heterocycl. Chem.* **1996**, *33*, 1.
Martins, M.A.P.; Freitag, R.A.; Flores, A.F.C.; Zanatta, N. *Synthesis* **1995**, 1491.
Martins, M.A.P.; Braibante, M.E.F.; Clar, G. *J. Heterocycl. Chem.* **1993**, *30*, 1159.

(2) Zanatta, N.; Pacholski, I.L.; Blanco, I.; Martins, M.A.P. *J.Braz.Chem.Soc.* **1991**, *2*, 118.
Zanatta, N.; Madruga, C.C.; Clerici, E.; Martins, M.A.P. *J. Heterocycl. Chem.* **1995**, *32*, 735.
Zanatta, N,; Cortelini, M.F.M.; Carpes, M.J.S.; Bonacorso, H.G.; Martins, M.A.P. *J. Heterocycl. Chem.* **1997**, *34*, 509.
Bonacorso, H.G.; Bittencourt, S.T.; Wastowski, A.D.; Wentz, A.P.; Zanatta, N.; Martins, M.A.P. *Tetrahedron Lett.* **1996**, *37*, 9155.
Zanatta, N.; Fagundes, M.R.; Ellensohn, R.; Marques, M.; Bonacorso, H.G.; Martins, M.A.P. *J. Heterocycl. Chem.* **1998**, *35*, 451.

(3) Effenberger, F.; Schönwälder, K.-H. *Chem. Ber.* **1984**, *117*, 3270.
Effenberger, F.; Maier, R.; Schönwälder, K.-H.; Ziegler, T. *Chem. Ber.* **1982**, *115*, 2766.
Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 295.

(4) Hojo, M.; Masuda, R.; Kokuryo, Y.; Shioda, H.; Matsuo, S. *Chem. Lett.* **1976**, 499.
Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1986**, 1013.
Hojo, M.; Masuda, R.; Sakagushi, S.; Takagawa, M. *Synthesis* **1986**, 1016.

(5) Martins, M.A.P.; Colla, A.; Clar, G.; Fischer, P.; Krimmer, S. *Synthesis* **1991**, *6*, 483.
Martins, M.A.P.; Siqueira, G.M.; Flores, A.F.C.; Clar, G.; Zanatta, N. *Química Nova* **1994**, *17*, 24.
Martins, M.A.P.; Flores, A.F.C.; Siqueira, G.M.; Freitag, R.; Zanatta, N. *Química Nova* **1994**, *17*, 298.

(6) Hauser, C.R.; Swamer, F.W.; Ringler, B.I. *J. Am. Chem. Soc.* **1948**, *70*, 4023.
Hamrick Jr., P.J.; Hauser, C.R. *J. Org. Chem.* **1959**, *24*, 583.
Snyder, H.R.; Brooks, L.A.; Shapiro, S.H. *Org. Syn. Coll. Vol.* **1943**, *2*, 531
Stetter, H.; Dierichs, W. *Ber.* **1952**, *85*, 1061.
Manyik, R.M.; Frostick, F.C.; Sanderson, J.J.; Hauser, C.R. *J. Am. Chem. Soc.* **1953**, *75*, 5030.

(7) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

(8) Unless otherwise indicated all common reagents and solvents were used as obtained from commercial suppliers without further purification. Yields listed in the Table are of isolated compounds and all boiling points are uncorrected. Elemental analysis was carried out on an Elemental Analysensysteme Vario EL apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-200 (^{1}H at 200.13 MHz and ^{13}C at 50.32 MHz), 298 K, digital resolution of 0.01 ppm, 0.5 M in chloroform-d_1/TMS.

Article Identifier:
1437-2096,E;1999,0,06,0789,0791,ftx,en;S08598ST.pdf