1,4-Conjugate addition of higher-order cyanocuprates to 3-alkyl substituted 2(5*H*)-furanones

Felix S. Pashkovsky,*[a] Fedor A. Lakhvich,[a] Alfredo Ricci[b] and Mauro Comes-Franchini[b]

[a] *Institute of Bioorganic Chemistry, Academy of Sciences of Belarus, 220141 Minsk, Republic of Belarus. Fax: +7 0172 63 7274; e-mail: evk@ns.iboch.ac.by*

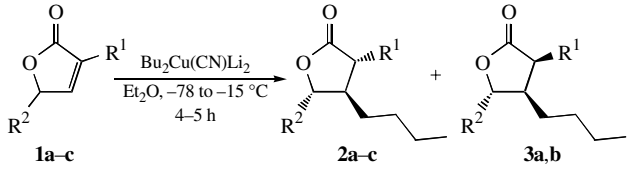
[b] *Dipartimento di Chimica Organica "A.Mangini", Facoltà di Chimica Industriale, Università di Bologna, 40136 Bologna, Italy. Fax: +39 051 209 3654; e-mail: ricci@ms.fci.unibo.it*

10.1070/MC2001v011n03ABEH001397

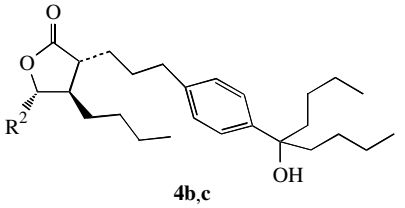
The results of model investigations concerning 1,4-addition of higher-order cyanocuprate $(n\text{-Bu})_2\text{Cu(CN)Li}_2$ to 3-alkyl-substituted butenolides are presented.

The 1,4-conjugate addition of different nucleophiles to 2(5*H*)-furanones (butenolides) is widely used for preparing compounds with a γ-butyrolactone ring.[1] Among Michael donors, organocopper reagents are of special importance because their nucleophilic addition to unsubstituted[2] or 5-alkyl-substituted butenolides[3] is a key step in the synthesis of naturally occurring products and their congeners. Surprisingly, almost nothing is known about the 1,4-addition of organocopper species to 3-alkyl-substituted butenolides in which an alkyl moiety is directly attached to the conjugated double bond of the heterocycle. Only one example of the Michael addition of the diarylmethane anion to 3-methyl-2(5*H*)-furanone in the presence of catalytic amounts of copper(I) iodide has been described.[4]

In connection with the synthesis of biologically active 10-oxa-prostaglandin analogues, we required a method for 1,4-conjugate addition of alkyl and alkenyl moieties to the butenolides with a preformed α-prostanoid chain. Therefore, firstly we attempted model investigations concerning the Michael addition of organocopper reagents to 3-alkyl-substituted 2(5*H*)-furanones. In our hands, the use of butyllithium in the presence of catalytic amounts of copper(I) iodide,[4] as well as the corresponding Gilman reagent, in this reaction was unsatisfactory. This is in accordance with the published data concerning low reactivity of α,β-unsaturated esters[5] and 5-alkyl-2(5*H*)-furanones[3] towards lower-order dialkyl cuprates. On the contrary, higher-order cyanocuprates are suitable reagents for this synthetic purpose.



1a–c **2a–c** **3a,b**



4b,c

a $R^1 = Me$, $R^2 = H$

b $R^1 = -(CH_2)_3-C_6H_4-CO_2Me$, $R^2 = H$

c $R^1 = -(CH_2)_3-C_6H_4-CO_2Me$, $R^2 = Me$

In this communication, we report the results of our investigations concerning the 1,4-addition of higher-order dibutylcyanocuprate $(n\text{-Bu})_2\text{Cu(CN)Li}_2$ to the 3-alkyl-substituted butenolides. The presence of oxygen in the five-membered ring reduces the reactivity of butenolides as Michael acceptors as compared to their carbocyclic counterparts.[3,5] We have found that the use of diethyl ether as a solvent in this reaction is essential. When THF or a mixture of diethyl ether and THF was employed, the reaction proceeded very slowly with almost quantitative recovery of the starting materials. Even in diethyl ether, higher temperatures (gradual increase from –75 to –15 °C) and prolonged reaction times (4–5 h) are necessary for completion of the reaction. The 1,4-addition of an alkyl moiety to 5-unsubstituted butenolides results in the formation of *cis*- and *trans*-isomers of the corresponding 3,4-disubstituted γ-butyrolactones, the *trans*-isomers being the major components. Elongation of a 3-alkyl substituent in the butenolide leads to an increased concentration of the *trans*-isomer. For example, the reaction of 3-methylfuran-2(5*H*)-one **1a** with 1.2 equiv. of higher-order dibutylcyanocuprate gives rise to the corresponding mixture of diastereomeric lactones **2a** and **3a** in 80% combined yields; the *cis*:*trans* ratio of **2a**/**3a** is 1.1:2.0. The *cis*-isomer showed a lower vicinal coupling constant $J_{\text{H-3/H-4}}$ 7.6 Hz in the ^{1}H NMR spectrum as compared with that of the *trans*-isomer (11.5 Hz). The 3-alkylaryl-substituted butenolide **1b** reacts with 1.2 equiv. of the same cuprate to give a mixture of diastereomeric 3-arylalkyl-4-butyl lactones **2b** and **3b** (71% yield) separable by column chromatography in an approximate *cis*:*trans* ratio of **2b**/**3b** = 1:3. The stereochemical assignment of **2b**, **3b** is based on the observation that $J_{\text{H-4/H-5}}$ for the *trans*-isomers is higher (8.5 Hz for $J_{a/a}$ and 7.0 Hz for $J_{a/e}$) as compared with those for the *cis*-isomers (6.0 and 5.5 Hz, respectively). On the contrary, in the case of sterically hindered 3,5-dialkyl-substituted butenolide **1c**, 1,4-addition of a butyl group proceeded stereoselectively to give only all-*trans*-trialkyl lactone **2c** in 66% yield. The vicinal coupling constant $J_{\text{H-5/H-4}}$ 8.4 Hz in the ^{1}H NMR spectrum of lactone **2c** supports the *trans*-orientation of methyl and butyl substituents.[6]

It follows from these experiments that the reaction of an almost equal amount of higher-order cyanocuprate with butenolides bearing an ester group in the side chain is chemoselective and extremely useful for the selective transformations of functionalised 2(5*H*)-furanones. Only small amounts of exhaustively alkylated products **4b**,**c** (4 and 7%, respectively) were isolated from the reaction mixtures. Trialkylated materials **4b**,**c** are the main products when a large excess (3–4 equiv.) of the cuprate reagent is used.†

† *General procedure*. To a stirred slurry of 54 mg (0.6 mmol) of CuCN in 8 ml of diethyl ether cooled at –78 °C, in an argon atmosphere, 0.75 ml (1.2 mmol) of a 1.6 M BuLi solution in hexane was added dropwise with a syringe. Then, the reaction mixture was allowed to gradually warm up to –30 °C. During this time, the clear yellowish solution of higher-order cyanocuprate was formed. To the resulting solution of the complex cooled to –78 °C 50 mg (0.5 mmol) of 3-methyl-2(5*H*)-furanone **1a** in 2 ml of diethyl ether was added dropwise with a syringe. In the case of butenolides **1b**,**c** sparingly soluble in Et_2O, 0.5 mmol of a compound was added to the reaction vessel in one portion under a stream of argon. The reaction temperature was gradually raised from –78 °C to –15 °C for 4–5 h with stirring. The reaction mixture was cooled again to –78 °C and quenched with saturated aqueous NH_4Cl. The cooling bath was removed, and the mixture was stirred until room temperature was reached. The ether layer was separated, the aqueous phase was extracted with diethyl ether (2×25 ml) and the combined ether extracts were dried with $MgSO_4$. The residue obtained after evaporation of the solvent was separated by column chromatography (silica gel, Et_2O–hexane).

The structures of **4b**,**c** were unambiguously assigned on the basis of ^{1}H NMR spectra and characteristic peaks of $[M - H_2O]^+$ ions in their mass spectra.‡ Interestingly, trialkylated product **4b** had only the *trans*-orientation of substituents at C-3 and C-4.

We also found that 3-alkyl-substituted butenolides are unreactive towards Grignard-derived higher-order cyanocuprate: even at room temperature the reaction with **1a** was extremely slow as compared to decomposition of the complex.

This work was supported by INTAS (grant no. 97-0084).

‡ For **2a**: colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, 3H, Me, *J* 7.0 Hz), 1.25 (d, 3H, Me, *J* 7.6 Hz), 1.25–1.48 (m, 6H, 3CH_2), 2.03–2.15 (m, 1H, H-4), 2.15 (dq, 1H, H-3, *J* 11.5, 7.6 Hz), 3.77 (dd, 1H, H-5, *J* 8.5, 8.5 Hz), 4.38 (dd, 1H, H-5, *J* 8.5, 7.0 Hz). IR (CCl_4, ν/cm^{-1}): 1777 (C=O lactone). MS, *m*/*z*: 156 $[M]^+$. Found (%): C, 69.09; H, 10.29. Calc. for $C_9H_{16}O_2$ (%): C, 69.19; H, 10.32.

For **2b**: colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, 3H, Me, *J* 7.0 Hz), 1.16–1.43 (m, 6H, 3CH_2), 1.50–1.65 (m, 1H), 1.70 (m, 2H, CH_2), 1.79–1.93 (m, 1H), 2.11–2.25 (m, 2H, H-4, H-3), 2.70 (t, 2H, CH_2Ar, *J* 7.5 Hz), 3.78 (dd, 1H, H-5, *J* 8.5, 8.5 Hz), 3.88 (s, 3H, CO_2Me), 4.35 (dd, 1H, H-5, *J* 8.5, 7.0 Hz), 7.24 (d, 2H_{arom}, *J* 8.4 Hz), 7.95 (d, 2H_{arom}, *J* 8.4 Hz). IR (CCl_4, ν/cm^{-1}): 1780 (C=O lactone), 1720 (C=O ester), 1605. MS, *m*/*z*: 318 $[M]^+$. Found (%): C, 71.64; H, 8.49. Calc. for $C_{19}H_{26}O_4$ (%): C, 71.67; H, 8.23.

For **2c**: colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 (t, 3H, Me, *J* 6.5 Hz), 1.18–1.36 (m, 4H, 2CH_2), 1.39 (d, 3H, Me, *J* 6.3 Hz), 1.48 (m, 2H, CH_2), 1.68–1.80 (m, 4H, 2CH_2), 1.84–1.96 (m, 1H, H-4), 2.28–2.36 (m, 1H, H-3), 2.70 (m, 2H, CH_2Ar), 3.90 (s, 3H, CO_2Me), 4.12 (dq, 1H, H-5, *J* 8.4, 6.3 Hz), 7.26 (d, 2H_{arom}, *J* 8.4 Hz), 7.96 (d, 2H_{arom}, *J* 8.4 Hz). IR (CCl_4, ν/cm^{-1}): 1774 (C=O lactone), 1724 (C=O ester), 1609. MS, *m*/*z*: 332 $[M]^+$. Found (%): C, 72.40; H, 8.44. Calc. for $C_{20}H_{28}O_4$ (%): C, 72.26; H, 8.49.

For **3a**: colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, 3H, Me, *J* 7.0 Hz), 1.16 (d, 3H, Me, *J* 7.6 Hz), 1.27–1.48 (m, 4H), 1.58–1.71 (m, 2H), 2.47 (m, 1H, H-4), 2.66 (quint, 1H, H-3, *J* 7.6, 7.6 Hz), 4.00 (dd, *J* 8.5, 5.5 Hz, 1H, H-5), 4.27 (dd, 1H, H-5, *J* 8.5, 6.0 Hz). IR (CCl_4, ν/cm^{-1}): 1777 (C=O lactone). MS, *m*/*z*: 156 $[M]^+$. Found (%): C, 68.82; H, 10.31. Calc. for $C_9H_{16}O_2$ (%): C, 69.19; H, 10.32.

For **3b**: colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (t, 3H, Me, *J* 7.0 Hz), 1.10–1.35 (m, 6H, 3CH_2), 1.40–1.53 (m, 1H), 1.61–1.75 (m, 2H, CH_2), 1.80–1.93 (m, 1H), 2.38–2.55 (m, 2H, H-4, H-3), 2.71 (m, 2H, CH_2Ar), 3.89 (s, 3H, CO_2Me), 4.04 (dd, 1H, H-5, *J* 8.5, 5.5 Hz), 4.19 (dd, 1H, H-5, *J* 8.5, 6.0 Hz), 7.24 (d, 2H_{arom}, *J* 8.4 Hz), 7.95 (d, 2H_{arom}, *J* 8.4 Hz). IR (CCl_4, ν/cm^{-1}): 1780 (C=O lactone), 1720 (C=O ester), 1605. MS, *m*/*z*: 318 $[M]^+$. Found (%): C, 71.61; H, 8.17. Calc. for $C_{19}H_{26}O_4$ (%): C, 71.67; H, 8.23.

References

1 (*a*) T. Jaworsky, W. Kolodzejek, J. Prejzner and M. Wlostowsky, *Polish J. Chem*., 1981, **55**, 1321; (*b*) V. Alcazar, J. R. Moran and J. de Mendoza, *Tetrahedron Lett*., 1995, **36**, 3941; (*c*) M. Fiorenza, A. Ricci, M. N. Romanelli, M. Taddei, P. Dembech and G. Seconi, *Heterocycles*, 1982, **19**, 2327; (*d*) S. W. McCombie, W. Stuart, J. R. Tagat, W. A. Metz, D. Nazareno and M. S. Puar, *Tetrahedron*, 1993, **49**, 8073; (*e*) P. Lakshmipathi and A. W. R. Rao, *Tetrahedron Lett*., 1997, **38**, 2551.
2 S. Tsuboi, J.-I. Sakamoto, H. Jamashita, T. Sakai and M. Utaka, *J. Org. Chem*., 1998, **63**, 1102.
3 A. M. Gilbert, R. Miller and W. D. Wulff, *Tetrahedron*, 1999, **55**, 1607.
4 K. Cruz-Almanza and F. P. Higareda, *Heterocycles*, 1992, **34**, 2323.
5 B. H. Lipshutz, *Synthesis*, 1987, 325.
6 C. Gunther and A. Mosandl, *Liebigs Ann. Chem*., 1986, 2112.

Received: 10th November 2000; Com. 00/1723

For **4b**: colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.77–0.92 (m, 9H, 3Me), 0.95–1.09 (m, 2H), 1.14–1.40 (m, 10H), 1.50–1.65 (m, 4H), 1.65–1.90 (m, 7H), 2.10–2.25 (m, 2H, H-4, H-3), 2.61 (t, 2H, CH_2Ar, *J* 7.5 Hz), 3.77 (dd, 1H, H-5, *J* 8.5, 8.5 Hz), 4.34 (dd, 1H, H-5, *J* 8.5, 7.0 Hz), 7.12 (d, 2H_{arom}, *J* 8.4 Hz), 7.25 (d, 2H_{arom}, *J* 8.4 Hz). IR (CCl_4, ν/cm^{-1}): 1781 (C=O lactone). MS, *m*/*z*: 384 $[M - H_2O]^+$. Found (%): C, 77.51; H, 10.49. Calc. for $C_{26}H_{42}O_3$ (%): C, 77.56; H, 10.51.

For **4c**: colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.80–0.98 (m, 9H, 3Me), 0.98–1.10 (m, 2H), 1.15–1.36 (m, 10H), 1.38 (d, 3H, Me, *J* 6.3 Hz), 1.43–1.53 (m, 2H), 1.56–1.65 (m, 2H), 1.65–1.91 (m, 7H), 2.27–2.35 (m, 1H, H-3), 2.56–2.76 (m, 3H), 4.13 (dq, 1H, H-5, *J* 8.4, 6.3 Hz), 7.13 (d, 2H_{arom}, *J* 8.4 Hz), 7.28 (d, 2H_{arom}, *J* 8.4 Hz). IR (CCl_4, ν/cm^{-1}): 1774 (C=O lactone). MS, *m*/*z*: 398 $[M - H_2O]^+$. Found (%): C, 77.75; H, 10.65. Calc. for $C_{27}H_{44}O_3$ (%): C, 77.84; H, 10.64.