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Effective one-pot synthesis of 2,3-dialkyl-1,4-dicyclopropylbutane-1,4-diones catalyzed by Cp_2TiCl_2

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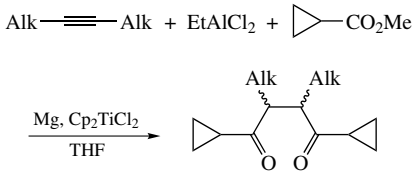
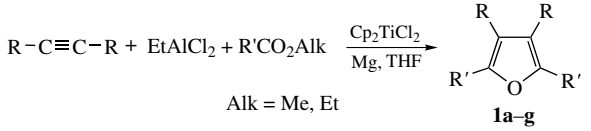
2,3-Dialkyl-l,4-dicyclopropylbutane-1,4-diones were prepared in one pot from symmetrical acetylenes, ethylaluminum dichloride and methyl cyclopropanecarboxylate in the presence of magnesium metal and Cp_2TiCl_2 (10 mol%) as a catalyst in 62–66% yield. Comparison of 1,4-dicyclopropylbutane-1,4-diones with other analogues to form furans in the course of the Paal–Knorr reaction was made by quantum chemical DFT calculations.



1,4-Diketones are important intermediates for the synthesis of cyclopentenones and heterocyclic compounds such as furans, pyrroles, thiophenes and pyridazines.[1] Their synthesis has been carried out using a variety of methods,[1,2] including the benzoin condensation between aldehydes and Michael acceptors catalyzed by cyanide or thiazolium salts.[1(*d*),3] Acylation of organostannanes with acid chlorides in the presence of palladium catalyst gives ketones in a general way. The corresponding reaction with alkenyl stannanes affords α,β-unsaturated ketones in moderate to good yields.[4] Gold-catalyzed oxidative dimerization of propargylic acetates giving 1,4-diones has been discussed.[5] Other synthetic routes to 1,4-diketones have also been reported.[6]

Here, we propose a new convenient synthesis of 2,3-dialkyl-l,4-dicyclopropylbutane-1,4-diones. Recently, we have reported that dialkyl-substituted symmetrical acetylenes (hex-3-yne, oct-4-yne, dec-5-yne) react with $EtAlCl_2$ in the presence of (cyclo)-alkylcarboxylic esters, metallic Mg and Cp_2TiCl_2 catalyst (alkyne : [Al] : ester : Mg : [Ti] = 1 : 2 : 2 : 2 : 0.1, THF, 60 °C, 6 h) to produce tetrasubstituted furans **1a–g** in 68–85% yields (Scheme 1).[7,8]

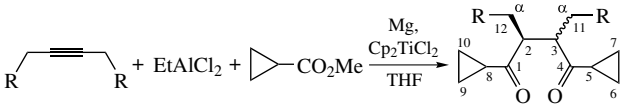


a R = Et, R′ = Me
b R = Pr, R′ = Me
c R = Bu, R′ = Me
d R = Pr, R′ = Et
e R = Pr, R′ = cyclobutyl
f R = Pr, R′ = cyclopentyl
g R = Pr, R′ = cyclohexyl

Scheme 1

Our further studies have shown that, in contrast to C_4–C_6 cycloalkanecarboxylates, methyl cyclopropanecarboxylate under the same reaction conditions gives rise to 2,3-dialkyl-1,4-dicyclopropyl-1,4-diketones **2a–c** in 62–66% yields (Scheme 2).[9]

The ^{13}C and ^1H NMR spectra of each of compounds **2a–c** contain two sets of signals indicating the presence of *d*,*l* and *meso* diastereomers in 2 : 3 ratio. The assignment of signals for



2a R = Et
2b R = Me
2c R = Pr

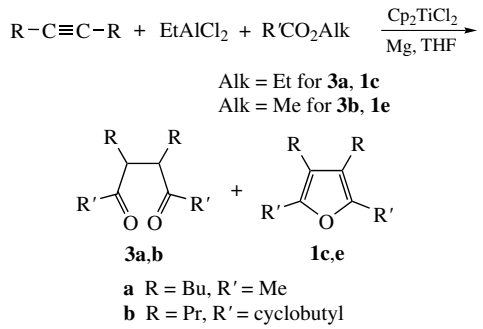
Scheme 2

each stereomer was made on the basis of COSY, HSQC and HMBC experiments using the spectral criteria described for 3,4-dialkyl-2,5-diones.[10] Chemical shifts of the carbon atoms in *meso* isomer located in 2- and 3-positions and also in α-position of the alkyl substituent appear in a lower field of the NMR spectra relative to the corresponding signals for *d*,*l*-isomer. Significant difference of the proton chemical shifts of the methylene group located in α-position to the asymmetric centers for *meso* diastereomer is the additional evidence for executed stereochemical identification.

Equivalence of the appropriate methylene protons in *d*,*l*-diastereomer is due to the existence of symmetrical forms at free rotation around the C^2–C^3 bond.†

† *2,3-Dialkyl-1,4-dicyclopropylbutane-1,4-diones* **2a–c**. The pre-dried and filled with dry argon glass reactor (50 ml) equipped with magnetic stirrer, reflux condenser and thermometer was charged with THF (15 ml), $EtAlCl_2$ (20 mmol, commercial grade, used as received), metallic Mg (powder, 20 mmol) and Cp_2TiCl_2 (1.0 mmol) at 0 °C. The mixture was stirred for 1 h, then acetylene (10 mmol) and methyl cyclopropanecarboxylate (20 mmol) were added. Temperature was raised up to 60 °C and the reaction mixture was stirred additionally for 6 h. After the reaction was complete, the mixture was cooled under argon to 0 °C. Then, diethyl ether (10–15 ml) was added and the mixture was hydrolyzed with dilute (7–10%) hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted twice with diethyl ether (2×20 ml). The combined extracts and organic layer were washed with $NaHCO_3$ solution until neutral and dried over $MgSO_4$. The final products were isolated by vacuum distillation. Spectral assignment for *d*,*l*- and *meso*-isomers were made on the basis of analysis of the fractions enriched in one isomer.

We found that similar 1,4-diketones **3** were the close precursors of furans **1** in the reaction of symmetrical acetylenes with $EtAlCl_2$ and carboxylates catalyzed by Cp_2TiCl_2 (Scheme 3). This is in accordance with the mechanism of Paal–Knorr reaction in the presence of Lewis acids.[11] Thus, for example, in the sample taken in 1 h after the beginning of the reaction, 1,4-diketones **3a**,**b** (**1c**,**e**:**3a**,**b** = 3:2) were detected, along with substituted furans **1c**,**e** and starting materials. Compounds **3a**,**b** were completely transformed into furans **1c**,**e** within 6 h (see Scheme 3).

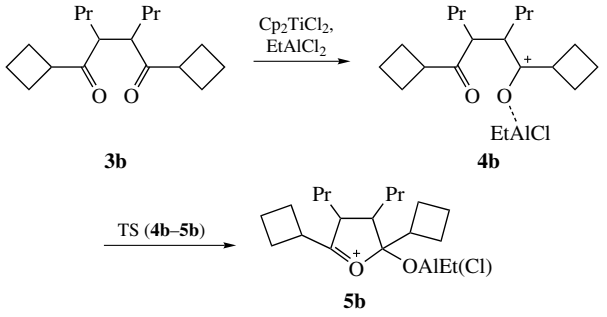


Scheme 3

In order to clarify the dependence of chemoselectivity of the cyclization reaction of 1,4-diketones into the corresponding furans on the nature of the starting substrate we have investigated potential energy surface of the reactions involving two diketones (1,4-dicyclopropyl-2,3-dipropylbutane-1,4-dione and 1,4-dicyclobutyl-2,3-dipropylbutane-1,4-dione) and $EtAlCl_2$ using quantum chemical methods.‡ The detailed theoretical study of the mechanism for the formation of the five-membered heterocycles from 1,4-dicarbonyl compounds (the Paal–Knorr reaction) has been earlier undertaken by B. Mothana and R. J. Boyd on the example of the pyrrole synthesis.[12] The proposed mechanism, based on the kinetics studies of the reactions of 3,4-dimethylhexane-2,5-dione with the primary amines[13,14] and acids,[15] leading to substituted pyrroles and furans, was consistent with the experimental data.

To clarify the observed chemoselectivity we have examined the key stage of the cyclization reaction of 1,4-dicyclobutyl-2,3-dipropylbutane-1,4-dione **3b**.

Considering the literature data,[7,12,16,17] we hypothesized that the interaction between **3b** and Cp_2TiCl_2 catalyst followed by subsequent transmetallation of the resulting adduct with $EtAlCl_2$ leads to the formation of intermediate **4b** (Scheme 4).



Scheme 4

Our DFT studies have shown that the transformation of **4b** to **5b** represents the thermodynamically favorable process since the calculated Gibbs energy for this reaction is negative (ΔG = = –26.4 kcal mol^{-1}). Scanning the potential energy surface along the cyclization reaction of **3b** revealed the presence of maximum, whose corresponding optimized structure is represented in Figure 1. The activation barrier for this reaction was low ($\Delta G^{\neq}$ = = 11.4 kcal mol^{-1}). These observations confirm the possibility of forming the furan cycle **5b**. However, it proved impossible to localize such a transition state and minimum of type **5b** for the process involving 1,4-dicyclopropyl analogue **2a**. Apparently, cyclopropyl substituents essentially accelerate solvolytic processes thus preventing further transformations of **2a** to form **5a**.[22]

Ring opening decelerates solvolysis and thus makes formation of furan possible. The numerous reactions where the cyclopropane ring opening is preceded by prior reaction with protonic or Lewis acids are well-known and proceed smoothly.[23] We have

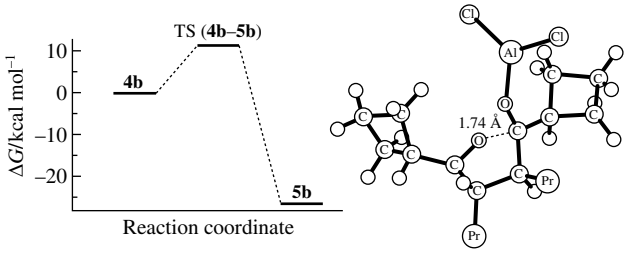


Figure 1 The energy diagram of the reaction **4b**→**5b** and DFT/PBE optimized structure for the TS (**4b–5b**) (ν = 362.8i cm^{-1}).

1,4-Dicyclopropyl-2,3-dipropylbutane-1,4-dione **2a**, *d,l-meso* isomer mixture. Yield 65%, bp 120–121 °C (1 mbar). MS, *m/z*: 250 $[M]^+$. Found (%): C, 76.72; H, 10.32. Calc. for $C_{16}H_{26}O_2$ (%): C, 76.75; H, 10.47.

For *d,l*-**2a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80–0.92 (m, 10H, Me, $C^{6,9}H_a$, $C^{7,10}H_a$), 0.93–0.97 (m, 4H, $C^{6,9}H_b$, $C^{7,10}H_b$), 1.15–1.21 (m, 2H, CH_a), 1.31–1.36 (m, 2H, CH_b), 1.55–1.66 (m, 4H, $C^{11,12}H_2$), 1.98–2.03 (m, 2H, $C^{5,8}H$), 3.01–3.02 (m, 2H, $C^{2,3}H$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.80 and 11.99 ($C^{6,7,9,10}$), 15.09 (Me), 20.71, 21.75 ($C^{5,8}$), 31.48 ($C^{11,12}$), 53.34 ($C^{2,3}$), 213.63 ($C^{1,4}$).

For *meso*-**2a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80–0.92 (m, 10H, Me, $C^{6,9}H_a$, $C^{7,10}H_a$), 1.07 (m, 4H, $C^{6,9}H_b$, $C^{7,10}H_b$), 1.22–1.29 (m, 4H, CH_2), 1.35–1.40 (m, 2H, $C^{11,12}H_a$), 1.55–1.66 (m, 2H, $C^{11,12}H_b$), 1.98–2.03 (m, 2H, $C^{5,8}H$), 2.97–3.02 (m, 2H, $C^{2,3}H$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.14 and 12.21 ($C^{6,7,9,10}$), 14.84 (Me), 21.38, 21.82 ($C^{5,8}$), 33.98 ($C^{11,12}$), 55.12 ($C^{2,3}$), 213.53 ($C^{1,4}$).

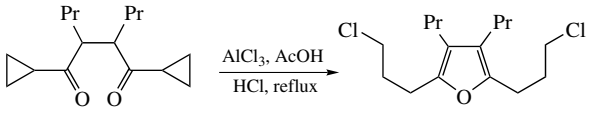
For *meso*-**2b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85–0.90 (m, 6H, Me), 0.91–0.95 (m, 4H, $C^{6,9}H_a$, $C^{7,10}H_a$), 1.06–1.11 (m, 4H, $C^{6,9}H_b$, $C^{7,10}H_b$), 1.48–1.53 (m, 2H, $C^{11}H_a$), 1.60–1.64 (m, 2H, $C^{11}H_b$), 1.98–2.08 (m, 2H, $C^{5,8}H$), 2.92–3.00 (m, 2H, $C^{2,3}H$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.78 (Me), 11.41 and 11.43 ($C^{6,7,9,10}$), 21.24 ($C^{5,8}$), 24.09 ($C^{11,12}$), 56.33 ($C^{2,3}$), 213.47 ($C^{1,4}$).

2,3-Dibutyl-1,4-dicyclopropylbutane-1,4-dione **2c**, *d,l-meso* isomer mixture. Yield 62%, bp 137–138 °C (1 mbar). MS, *m/z*: 278 $[M]^+$. Found (%): C, 76.62; H, 10.74. Calc. for $C_{18}H_{30}O_2$ (%): C, 77.65; H, 10.86.

For *d,l*-**2c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80–0.92 (m, 10H, Me, $C^{6,9}H_a$, $C^{7,10}H_a$), 0.96–0.99 (m, 4H, $C^{6,9}H_b$, $C^{7,10}H_b$), 1.22–1.33 (m, 8H, CH_2), 1.56–1.70 (m, 4H, $C^{11,12}H_2$), 1.98–2.05 (m, 2H, $C^{5,8}H$), 3.09–3.15 (m, 2H, $C^{2,3}H$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.08 and 11.23 ($C^{6,7,9,10}$), 13.89 (Me), 21.00 ($C^{5,8}$), 22.95, 28.11 ($C^{11,12}$), 28.77, 53.22 ($C^{2,3}$), 213.61 ($C^{1,4}$).

For *meso*-**2c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80–0.92 (m, 10H, Me, $C^{6,9}H_a$, $C^{7,10}H_a$), 1.06–1.11 (m, 4H, $C^{6,9}H_b$, $C^{7,10}H_b$), 1.12–1.33 (m, 8H, CH_2), 1.35–1.45 (m, 2H, $C^{11,12}H_a$), 1.56–1.70 (m, 2H, $C^{11,12}H_b$), 1.98–2.05 (m, 2H, $C^{5,8}H$), 2.95–3.02 (m, 2H, $C^{2,4}H$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.46 and 11.50 ($C^{6,7,9,10}$), 13.80 (Me), 21.00 ($C^{5,8}$), 22.26, 29.52 ($C^{11,12}$), 30.67, 55.25 ($C^{2,3}$), 213.53 ($C^{1,4}$).

‡ All calculations were carried out using a PRIRODA-06 program.[18,19] Geometric parameter optimization, vibrational frequency analysis, and calculation of entropy and thermodynamic corrections to the total energy of the compounds were performed on the DFT level with the Perdew–Burke–Ernzerhof (PBE) functional in combination with a 3ζ basis set.[19] Thermodynamic parameters and activation energies were determined at 298.15 K. The minima were confirmed through the calculation of the force constant (Hessian) matrix and the analysis of the resulting frequencies. Visualization of quantum chemical data was carried out with the programs ChemCraft.[21]



2a **6**

Scheme 5

carried out the reaction between **2a** and $AlCl_3$ under strong reaction conditions in the presence of a mixture of concentrated hydrochloric and acetic acids.[24] As a result, 2,5-bis(3-chloropropyl)-3,4-dipropylfuran **6** was obtained in 92% yield (Scheme 5).[§]

In conclusion, a new selective method for the synthesis of 2,3-dialkyl-1,4-dicyclopropylbutane-1,4-diones from symmetric alkynes with $EtAlCl_2$ and methyl cyclopropanecarboxylate in the presence of Cp_2TiCl_2 catalyst has been developed. Comparative quantum chemical studies of the cyclization stage of aluminum-containing intermediates involving 1,4-dicyclopropyl-2,3-dipropylbutane-1,4-dione and 1,4-dicyclobutyl-2,3-dipropylbutane-1,4-dione have shown that the reaction cannot bring about adducts bearing cyclopropyl substituents that allows one to explain chemoselectivity of the reaction studied.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.04.015.

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§ *2,5-Bis(3-chloropropyl)-3,4-dipropylfuran* **6**. A mixture of concentrated hydrochloric acid (20 ml) and acetic acid (30 ml) was heated to boiling, and aluminum chloride (20 mmol) was added. Then, **2a** (10 mmol) in 25 ml of acetic acid was added dropwise. Heating was continued for 20 min, then the reaction mixture was poured into 100 ml of water and extracted with diethyl ether (3×30 ml). The organic layer was washed with saturated $NaHCO_3$ solution until neutral, and then dried over anhydrous Mg_2SO_4. The solvent was removed, and the residue was distilled *in vacuo*. Yield 92%, bp 170–171 °C (1 mbar). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, 6H, Me, *J* 8.0 Hz), 1.48 (sextet, 4H, CH_2, *J* 8.0 Hz), 2.04–2.11 (m, 4H, CH_2), 2.26 (t, 4H, CH_2, *J* 8.0 Hz), 2.69 (t, 4H, CH_2, *J* 8.0 Hz), 3.46 (t, 4H, CH_2, *J* 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.17, 22.36, 24.09, 25.72, 31.50, 44.44 (CH_2Cl), 120.09 ($C^{2,3}$), 147.28 ($C^{1,4}$). MS, *m*/*z*: 305 $[M]^+$. Found (%): C, 62.90; H, 8.41. Calc. for $C_{16}H_{26}Cl_2O$ (%): C, 62.95; H, 8.58.

For more details, see Online Supplementary Materials.

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