Scientific paper

Calorimetric Insight into Coupling between Functionalized Primary Alkyl Halide and Vinylic Organocuprate Reagent: Experimental Determination of Reaction Enthalpies in the Synthesis of (*R*)-Ethyl 3-(*tert*-butyldimethylsilyloxy) hex-5-enoate – a Key Lactonized Statin Side Chain Precursor

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Dedicated to the memory of the late Prof. Dr. Valentin Koloini

Abstract

The first calorimetric study of coupling between organocuprate, derived from Grignard reagent (vinyl magnesium chloride), and primary alkyl halide (e.g. (*S*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-4-iodobutanoate) has been conducted. This transformation is paramountly important for efficient preparation of (*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate – a key lactonized statin side chain precursor. The results obtained give thorough calorimetric insight into this complex low-temperature synthesis as well as a new understanding of the suggested reductive elimination of the final intermediates in the coupling reaction. Namely, the surprising unexpected spontaneous three-step exothermal event has been observed during controlled progressive heating of the mixture of the final intermediates to the room temperature. This phenomenon confirms that coupling between functionalized primary alkyl halide and vinylic organocuprate reagent is not a simple S_N2 substitution reaction. The presented study provides among others the first reported values of reaction enthalpies and corresponding adiabatic temperature rises of reaction mixture for all exothermic events that occurred in the (*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate synthesis. The obtained results ensure consequential thermal process safety knowledge which can be incorporated into safe process scale-up as well as design of reactor system with sufficient cooling capacity for industrial production of (*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate. Moreover, the results provide a basic guidance for other organocuprate coupling reaction systems.

Keywords: Grignard reagents, organocuprates, coupling reaction, reaction calorimetry, statins.

1. Introduction

Statins, or 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitors,[1] termed hypocholesterolemic agents, have become the most frequently prescribed and efficient drugs for the treatment of hypercholesterolemia[2] because of the compelling evidence of their effect on reducing the rates of cardiovascular events.[3] Initially discovered as fungal metaboli-

tes,[4] statins have evolved rapidly in the past 20 years to a refined synthetic analogues comprised of a heterocyclic core and a chiral 3,5-dihydroxy-6-heptenoic or heptanoic acid side chain. Nevertheless, the β-hydroxy lactone moiety remained unmodified because it was found that it is essential for biological activity of statins.[5] Examples of the marketed members of this group of compounds are fluvastatin,[6] pitavastatin,[7] worlds best selling drug atorvastatin,[8] and still growing blockbuster rosuvastatin.[9]

Many diverse synthetic approaches towards statins have been developed in the last two decades.[10] Nevertheless, quite recently we have pointed out a novel highly convergent approach, which could be used for statin preparation, by applying lactonized side chain precursor **1**.[11] Furthermore, we have recently reported an efficient preparation of chiral lactonized statin side chain precursors for the synthesis of synthetic statins wherein a key intermediate is (4*R*,6*S*)-4-(*tert*-butyldimethylsilyloxy)-6-(iodomethyl)-tetrahydropyran-2-one **2** (Figure 1).[12]

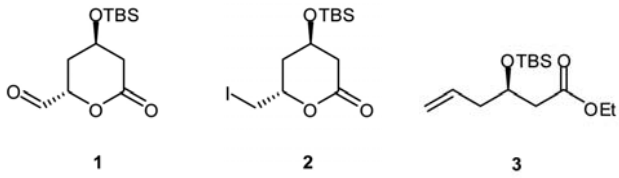
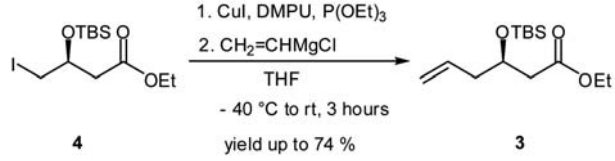


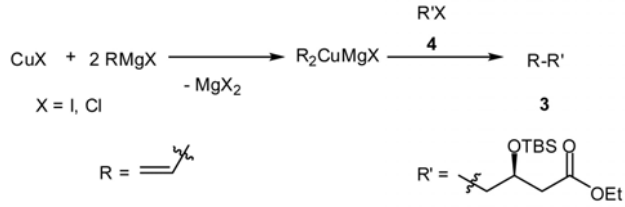
Figure 1. Key lactonized satin side chain intermediates.[11, 12]

The presented synthetic strategy, which affords iodolactone **2** in the highest yield yet, utilizes (*S*)-ethyl 4-chloro-3-hydroxybutanoate (CHB).[12] A key step in this reaction sequence is elaboration of (*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate (TBSH) **3** which is then converted to iodolactone **2** in two steps.[13] The TBSH **3** is prepared by procedure originally described by Sato *et al.* for (*S*)-enantiomer of TBSH **3**[14] and later by Numata *et al.* for (*R*)-enantiomer of TBSH **3**[15] where organocuprate is first prepared from vinylmagnesium bromide (VMB) in the presence of 3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and triethyl phosphite ($P(OEt)_3$) in tetrahydrofuran (THF). The formed divinylmagnesium cuprate (DVMCU) then reacts with (*S*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-4-iodobutanoate (TBSIB) **4** to give TBSH **3**.



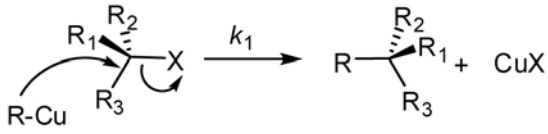
Scheme 1. Synthesis of (*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy) hex-5-enoate (TBSH) **3.**[12]

Although, we have performed some improvements and simplifications in this reaction (Scheme 1),[12] deeper insight into thermodynamics is needed for safe large scale utilization as well as for the better understanding of this complex organocuprate coupling since mechanism is not clearly established. The TBSH **3** is formed *via* coupling of DVMCU ($(CH_2=CH)_2CuMgCl$), derived from viniylmagnesiun chloride (VMC; $CH_2=CHMgCl$) and copper (I) iodide (CuI), with TBSIB **4** (Scheme 2).[16]



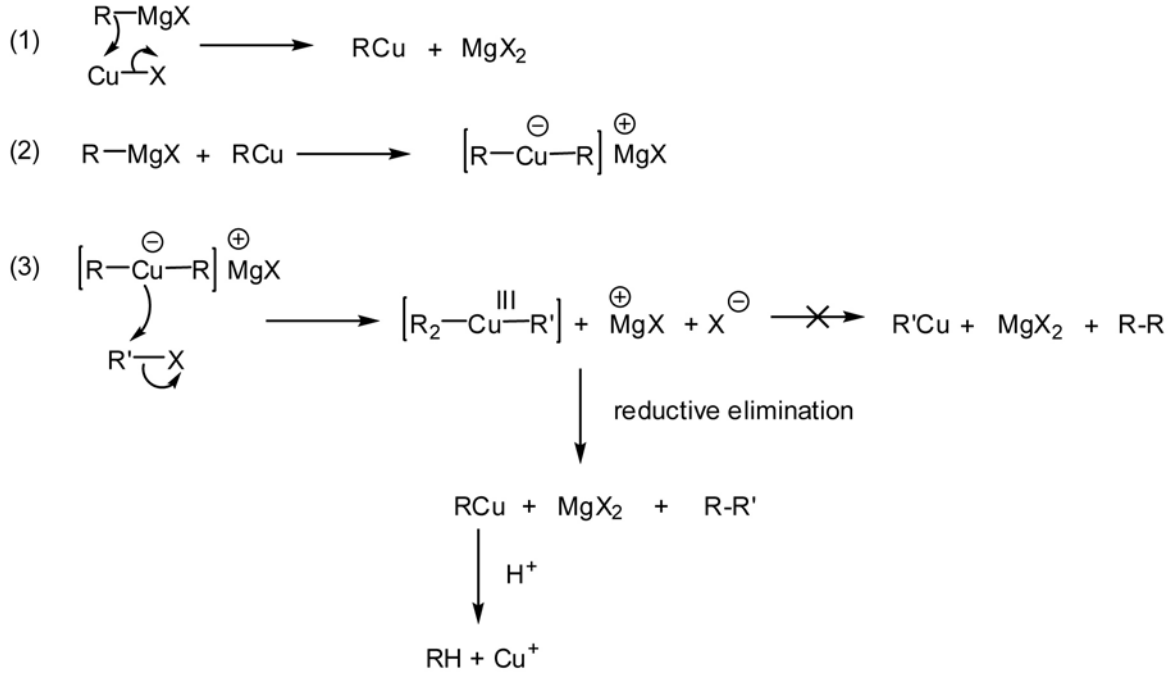
Scheme 2. Formation and coupling of DVMCU ($(CH_2=CH)_2CuMgCl$) with TBSIB **4**.

Organocuprates (R_2CuMgX species) are highly effective synthetic reagents for nucleophilic delivery of hard anionic nucleophiles such as vinyl and other carboanions to multifunctional substrates with sensitive functional groups such as ester moieties. Although organocuprates, derived from Grignard reagents are frequently prepared and used reagents, their structure, described as R_2CuMgX, is still not unambiguously determined in solution. This also leads to uncertainty in reaction mechanisms of these species. Namely, the structures of final copper-containing intermediates which yield products are generally unknown. Furthermore, the mechanism of copper-mediated substitution reactions is not fully understood and several possible mechanistic pathways have been suggested till now. The most straight forward suggested mechanism is simple S_N2 substitution reaction of electrophile (alkyl halide) with organocopper (R) anion (Scheme 3).[17]



Scheme 3. Direct s S_N2 substitution reaction.[17]

The most appealing suggestion for the coupling mechanism between organocopper species and alkyl halides assumes the formation of organocuprate R_2CuMgX from Grignard reagent and copper halide (Eqs. 1 and 2, Scheme 4) followed by the displacement of the leaving group with copper bearing the a formal negative charge and formation of trialkylcopper (III) intermediate (Eq. 3, Scheme 4).[17,18] The trialkylcopper (III) intermediate then



Scheme 4. Suggested mechanism of organocuprate coupling with alkyl halide via trialkylcopper(III) intermediate.[17]

undergoes reductive elimination to give the cross-coupling product R-R' and organocopper reagent RCu, which is then quenched with water solution.

Finally, radical SET mechanism has also been described and has been suggested for the alkylation reaction of secondary alkyl iodides where substitution reaction takes place in stereorandom fashion.[19] However, this possible mechanism is not relevant to the present study, since we are dealing with primary alkyl iodide **4**.

Since the mechanism of coupling is not entirely clear, application of organocopper chemistry on industrial scale requires better understanding or calorimetric evaluation for safety reasons in scale-up as well as in the optimization of reaction yield to afford this chemistry economically feasible. Therefore, thorough calorimetric insight into organocopper substitution reaction on saturated carbon atom which circumvents the lack of exact mechanism understanding for safe large scale preparation is needed.

Calorimetry is the science of measuring the heat of chemical reactions or physical changes.[20] Any process that results in heat being generated by or exchanged with the environment is a candidate for a calorimetric study. Since all chemical, physical and biological processes are accompanied by heat flow, calorimetry clearly has a broad range of applicability, ranging from drug design to quality control of process streams in the chemical and biochemical industry. Many different types of calorimeters exist and among them reaction calorimeter is the most widely used.[21] It is a calorimeter in which a chemical reaction is initiated within a closed insulated container. Reaction heats are measured and the total heat is obtained by integrating heat flow versus time. This is the standard used in industry to measure heats since industrial processes are engineered to run at constant temperatures. Reaction calorimetry can also be used to determine maximum heat release rate for chemical process engineering and for tracking the global kinetics of reactions. Over the past 35 years reaction calorimetry has also been used for the optimization of chemical processes.[22] Many of them have been examined closely and the in-depth process knowledge gained has saved costs. As reaction calorimeters range from a few milliliters to some liters reaction volume – using single reactor or multiple reactor systems, they cover the entire field of process development**.** Today, reaction calorimeter is the proven industrial standard in both the chemical and pharmaceutical industries.

The aim of the present study is to determine the reaction enthalpies and corresponding adiabatic temperature rises of reaction mixture for all exothermic events that occurred in the TBSH **3** synthesis, which is a complex sequence of low temperature chemical reactions between highly (moisture) sensitive intermediates, using high-quality reaction calorimeter.

2. Experimental

2. 1. Materials and Equipment

2. 1. 1. Materials

Copper (I) iodide (CuI; assay, $w \geq 98.0$ %; Fluka), dry tetrahydrofuran (THF, puriss., absolute, over molecu-

lar sieve ($w_{H_2O} \leq 0.005$ %), $w \geq 99.5$ %; density, $\rho = 0.889$ g mL^{-1}; Fluka), vinylmagnesium chloride (VMC) solution in THF (VMC solution; molar concentration of VMC, $c_{VMC} = 1.9$ mol L^{-1}; $\rho = 0.98$ g mL^{-1}; Chemetall), 3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; $w \geq 96.0$ %; $\rho = 1.06$ g mL^{-1}; Fluka), triethyl phosphite ($P(OEt)_3$; $w \geq 95$ %; $\rho = 0.955$ g mL^{-1}; Fluka), ammonium chloride (NH_4Cl; $w \geq 99.5$ %; Fluka), diisopropyl ether ($^iPr_2O$; $w \geq 98.0$ %; Sasol Solvents GmbH), sulphuric acid (H_2SO_4; $w \geq 95$ %; Merck KGaA), (*S*)-ethyl 4-chloro-3-hydroxybutanoate (CHB; $w \geq 98.0$ %; Molekula UK Ltd), acetone ($w \geq 99$ %; Brenntag CEE GmbH), sodium iodide (NaI; $w \geq 98$ %; Merck KGaA), sodium thiosulphate ($N_2S_2O_3$; $w \geq 99$ %; Merck KGaA), *tert*-butyl methyl ether (^{t}BuMeO; $w \geq 99.0$ %; Univar), imidazole (IMD; $w \geq 99$ %; Merck Schuchard OHG), dimehylformamide (DMF; $w \geq 99.0$ %; BASF SE), *tert*-butyldimethylsilyl chloride (TBSCl; $w \geq 96$ %; Sigma-aldrich Chemie GmbH) are commercially available and were used as received without further purification. (*R*)-Ethyl 3-(*tert*-butyldimethylsilyloxy)hex-5-enoate (TBSH) **3** and (*S*)-ethyl 3-(*tert*-butyldimethylsilyfoxy)-4-iodobutyrate (TBSIB; $w \geq 96$ % by GC; $\rho = 1.286$ g mL^{-1}) **4** were prepared according to the approach presented in our preliminary communication.[12] Details of these procedures are given in the experimental part described below.

2. 1. 2. Equipment

Reaction calorimeter RC1 has been used for calorimetric studies in our case. It is a computer-controlled, electronically safe-guarded lab reactor for the performance of isothermal and adiabatic reactions and the determination of thermal data and constants, their recording and mathematical evaluation balancing.[23] The complete RC1 system comprise the actual RC1 reaction calorimeter (with thermostat, stirrer, electronics cabinet), a glass chemical reactor ($V = 2$ L) with a glass cover for operation at ambient pressure and a personal computer. For control of the pumps or valves and to acquire additional measured values, a dosing controllers are attached.

Chemical processes or individual steps are performed on a two liter scale under conditions approaching reality and all important process variables such as temperature, dosing operations, mixing, thermal power of the reaction and heat transport data are determined and controlled. All components of the flexible system are so designed that the results obtained on a two liter scale can be scaled up to the plant conditions.

2. 2. Methods

2. 2. 1. Calorimetric Measurement Background

Majority of chemical reactions and physical operations (crystallization, evaporation, dissolution, dilution etc.) in production of pharmaceutical intermediates and active pharmaceutical ingredients either generate or consume heat. According to the thermodynamic principles, the enthalpies of those reactions (or physical operations), $\Delta_r H$, are basically defined as:

$$\Delta_r H = \frac{-Q_r}{n} = \frac{-\int_{t=0}^{t=t} \Phi_r(t)\mathrm{d}t}{n} \tag{1}$$

where Q_r – overall either released (positive sign) or consumed (negative sign) heat due to reaction, Φ_r – heat flow due to reaction, t – reaction time, and n – amount of key component.

Perhaps one of the most user-friendly as well as the most efficient unique commercially available process development engineering tools for the experimental determination of $\Phi_r(t)$ and hence, by integration over reaction time, Q_r is heat-flow reaction calorimeter RC1 (Mettler Toledo). Basically, a "Win RC" software of RC1 calculates Φ_r profile by making precise time-depended overall heat-flow balance around standard glass reactor wall. This balance can be mathematically expressed as:

$$\begin{aligned} \Phi_r &= \Phi_f + \Phi_a + \Phi_d + \Phi_l = \\ &= UA\left(\vartheta_{rm} - \vartheta_j\right) + m_{rm}c_{P,rm}\frac{\mathrm{d}\vartheta_{rm}}{\mathrm{d}t} + \\ &+ c_{P,d}\frac{\mathrm{d}m_{rm}}{\mathrm{d}t}\left(\vartheta_{rm} - \vartheta_d\right) + k\left(\vartheta_{rm} - \vartheta_{am}\right) \end{aligned} \tag{2}$$

where Φ_f – heat flow through reactor wall, Φ_a – heat flow accumulated in the reaction mixture, Φ_d – heat flow input due to dosing, Φ_l – heat flow to the environment through non-jacketed part of reactor, U – overall heat transfer coefficient, A – active heat transfer area, ϑ_{rm} – temperature of reaction mixture, ϑ_j – reactor jacket temperature, m_{rm} – mass of reaction mixture, $c_{P,rm}$ – specific heat capacity of reaction mixture, $c_{P,d}$ – specific heat capacity of added (dosed) material, ϑ_d – temperature of added (dosed) material, k – specific heat loss, and ϑ_{am} – ambient temperature.

It is evident from Eq. (2) that beside an accurate in-line measurement of ϑ_{rm} and ϑ_j the knowledge of other parameters and constants, especially U and $c_{P,rm}$, is crucial for a precise determination of Φ_r profile and consequently Q_r. Therefore, an automatic U and $c_{P,rm}$ determination should be performed preferably before and after the reaction at the time of classical RC1 experiment. These two experimentally determined pairs of U and $c_{P,rm}$ can be joined during the time of reaction in different modes. The most common and simple one is linear interpolation.

Briefly, when all heat flows in Eq. (2) are equal to zero or at least constant, the U can be determined by the standard calorimetric calibration procedure using an immersed electrical heater. A known amount of thermal power is introduced, typically over a period of 10 minutes, into the reaction mixture and the measured calibration heat flow, Φ_c, is stored. The heat realized due to activity of

calibration heater generates an average temperature difference between reaction mixture and reactor jacket, $\Delta\vartheta_{avr,rm,j}$, as result of heat-flow balancing over a known A of reactor wall. Therefore, the U can be calculated as:

$$U = \frac{\Phi_c}{A\Delta\vartheta_{avr,rm,j}} \quad (3)$$

In addition, an automatic calorimetric calibration procedure includes also determination of $c_{P,rm}$ using classical temperature ramp. The reaction mixture is either heated or cooled for $\Delta\vartheta_{rm}$ = 3 °C over a known time-period (typically 10 minutes) and afterwards the $c_{P,rm}$ is computed as:

$$c_{P,rm} = \frac{-UA\Delta\vartheta_{avr,rm,j}}{m_{rm}v_{rm}} \quad (4)$$

where v_{rm} – heating (positive sign) or cooling rate (negative sign) of reaction mixture.

The heat flow due to exothermic reaction is directly connected with thermal process safety issues especially if cooling system fails.[24] Namely, when a heat exchange between reactive system and its surroundings is not provided, the adiabatic conditions prevail. Consequently, the whole produced heat during reaction is used to increase the temperature of reaction mixture. Thus, the adiabatic temperature rise of reaction mixture, $\Delta\vartheta_{rm,ad}$, is proportional to the heat flow due to exothermic reaction and can be computed as:

$$\Delta\vartheta_{rm,ad} = \frac{Q_r}{m_{rm,f}c_{P,rm,f}} \quad (5)$$

where $m_{rm,f}$ – final (after reaction completed) mass of reaction mixture and $c_{P,rm,f}$ – final specific heat capacity of reaction mixture.

From process safety point of view, the $\Delta\vartheta_{rm,ad}$ is one of the most convenient and therefore commonly used thermal process safety indicators to expose the severity of exothermic reaction. Basically, the higher the $\Delta\vartheta_{rm,ad}$, the higher the final temperature of reaction mixture will be in case of cooling system failure. However, this thermal process safety indicator gives only information about thermal potential of exothermic reaction under adiabatic conditions and does not directly assure data about kinetics of the potential runway. Nevertheless, the dynamic ϑ_{rm} profile under adiabatic conditions can be determined either experimentally or more plainly and safely by simulation using Φ_r data obtained during calorimetric study under normal (usually isothermal) process conditions.

2. 3. Experimental Procedures

2. 3. 1. Kilo-lab Preparation of Key Intermediates

a) Kilo-lab Synthesis of TBSH 3.

To a vigorously stirred suspension of 166.6 g CuI (amount of CuI, n_{CuI} = 874 mmol) in 1.75 L of dry THF was added, at ϑ_{rm} = (–44–(–31)) °C in 15 minutes, 920 mL of VCM (amount of VMC, n_{VMC} = 1 748 mmol) followed by addition of 40 mL of dry THF. The obtained brown slurry was then stirred for 15 min followed by addition of 224.6 g of DMPU (amount of DMPU, n_{DMPU} = 1 748 mmol) at ϑ_{rm} = (–42.5–(–38)) °C. Afterwards, 320 mL of $P(OEt)_3$ (amount of $P(OEt)_3$, $n_{P(OEt)3}$ = 1 748 mmol) at ϑ_{rm} = (–40–(–36)) °C was added to the reaction mixture together with 20 mL of dry THF. The obtained mixture was then stirred for 30 min at ϑ_{rm} = –40 °C followed by addition of 325.4 g of TBSIB **4** (amount of TBSIB **4**, $n_{TBSIB\ 4}$ = 874 mmol) solution in 440 mL of THF at ϑ_{rm} = (–40–(–36)) °C in 15 minutes. The stirring was continued for 1 hour at ϑ_{rm} = (–40–(–35)) °C. Then the reaction mixture was left to warm spontaneously to ϑ_{rm} = 20 °C in 3.5 hours. Afterwards, the reaction mixture was cooled down to ϑ_{rm} = –1.5 °C and treated with 2.0 L of saturated aqueous NH_4Cl solution, and stirred at room temperature for 30 minutes. Product was extracted into $^{i}Pr_2O$ (1 × 1 600 mL of $^{i}Pr_2O$ + 5 × 500 mL of $^{i}Pr_2O$). Organic extracts were concentrated to 3 L of volume and the residue was washed with aqueous solution of H_2SO_4 (molar concentration of H_2SO_4, $c_{H_2SO_4}$ = 0.1 mol L^{-1}; 4 × 800 mL of H_2SO_4 solution), dried with $MgSO_4$ and the volatiles were removed under reduced pressure (p = 15 mbar) at ϑ_{rm} = 80 °C to afford 628.4 g of red-brown oily residue which contained 44 % of product by GC. This residue is purified further by vacuum distillation (ϑ_{rm} = (64–72) °C , p = (0.10–0.44) mbar) to give 161.5 g (yield, Y = 68 %) of TBSH **3** as a colorless oil (GC purity 96 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (ddt, J = 17.8, 9.6 and 7.2 Hz, 1H), 5.11–5.03 (m, 2H), 4.21 (quint., J = 6.8 Hz, 1H), 4.12 (qt, J = 7.1 and 1.5 Hz, 2H), 2.43 (d, J = 7.1 Hz, 1H), 2.43 (d, J = 5.4 Hz, 1H), 2.31–2.25 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 134.1, 117.6, 68.9, 60.2, 42.1, 42.1, 25.7, 17.9, 14.1, -4.6, -5.0. $[\alpha]^{25}_D$ = –35.5 (c 1, $CHCl_3$) (lit.[16] $[\alpha]^{28}_D$ = –32 (c 0.63, $CHCl_3$)).

b) Kilo-lab synthesis of TBSIB 4.

To a solution of 659 g of CHB (amount of CHB, n_{CHB} = 3.836 mol, mass fraction of CHB; w_{CHB} = 98 %) in 7.7 L of acetone was added 2.3 kg of NaI (amount of NaI, n_{NaI} = 15.34 mol) and mixture was stirred for 120 hours under reflux. Acetone was removed under reduced pressure to afford 2.95 kg of brownish oil which contained some precipitate. To this mixture 3 L of H_2O was added and 1.53 L of saturated aqueous $Na_2S_2O_3$ solution. The mixture was stirred at ϑ_{rm} = 30 °C till all the precipitate was dissolved followed by addition 2.75 L of H_2O and 2.3 L of ^{t}BuMeO. The mixture was vigorously stirred for 1 hour and the phases were separated. The water phase was additionally extracted with ^{t}BuMeO (2 × 1.15 L of ^{t}BuMeO). Combined organic extracts were washed with 0.8 L of H_2O and dried with $MgSO_4$. The volatiles were removed under reduced pressure at ϑ_{rm} = 40 °C to afford 995 g of

(*S*)-ethyl 4-iodo-3-hydroxybutanoate (IHB) as yellow oil which was 86 % pure by GC. This product is rather unstable and elimination of iodine can be observed over the time. Therefore, it is used in the next step without further purification. A product with purity of 98–99 % by GC for analytical purposes can be obtained by vacuum distillation (ϑ_{rm} = (73–89) °C, p = (0.180–0.330) mbar) of the crude product. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.17 (q, J = 7.2 Hz, 2H), 3.99 (m, 1H), 3.34 (dd, J = 10.3 and 5.2 Hz, 1H), 3.28 (dd, J = 10.3 and 5.7 Hz, 1H), 3.21 (br s, 1H), 2.67 (dd, J = 16.5 and 4.3 Hz, 1H), 2.58 (dd, J = 16.5 and 7.9 Hz, 1H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 67.4, 61.0, 40.7, 14.1, 12.0.

The oily IHB (mass of IHB, m_{IHB}= 949.55 g; amount of IHB, n_{IHB} = 3.68 mol) was dissolved in solution of 252.3 g of IMD (amount of IMD, n_{IMD} = 7.36 mol) in 7 L of dry DMF. Then 1.106 kg of NaI (n_{NaI} = 7.36 mol) was added at room temperature and suspension was cooled to ϑ_{rm} = 0 °C under argon atmosphere followed by addition of 838 g of TBSCl (amount of TBSCl, n_{TBSCl} = 5.56 mol) and 0.6 L of dry DMF. The mixture was stirred at ϑ_{rm} = 0 °C for 1.5 hours. Afterwards, the mixture was left to warm spontaneously to room temperature in 1.5 hours and was further stirred at room temperature for 15.5 hours. Then the mixture was cooled to ϑ_{rm} = 0 °C and quenched by 4.5 L of H_2O. After 2 hours stirring, 0.5 L of saturated aqueous $Na_2S_2O_3$ solution and 6.2 L of H_2O were added. The product was extracted with ^{t}BuMeO (4 × 2 L of ^{t}BuMeO). Organic extracts were combined and dried with $MgSO_4$. Volatiles were removed under reduced pressure to afford 1.65 kg of crude product as yellow oil. This oil was purified further by vacuum distillation (ϑ_{rm} = (80–89) °C , p = (0.15–0.31) mbar). Fractions that contained product with purity higher than 96 % by GC were combined to give 1.229 kg of brown oil. This oil was dissolved in 600 mL of ^{t}BuMeO and washed with saturated aqueous $Na_2S_2O_3$ solution (2 × 500 mL of $Na_2S_2O_3$ solution). Organic phase was additionally washed with 500 mL of H_2O and dried with $MgSO_4$. The volatiles were removed under reduced pressure (p = 20 mbar) at ϑ_{rm} = 60 °C to give 1.1935 kg of TBSIB **4** (mass fraction of TBSIB 4, $w_{TBSIB\ 4}$ = 97 %) as a clear yellow oil (w = 96.1 % by GC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.13 (qd, J = 7.2 and 2.1 Hz, 2H), 4.01 (m, 1H), 3.28 (dd, J = 10.2 and 4.2 Hz, 1H), 3.24 (dd, J = 10.2 and 6.0 Hz, 1H), 2.66 (dd, J = 15.3 and 4.8 Hz, 1H), 2.51 (dd, J = 15.3 and 7.2 Hz, 1H), 1.26 (t, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 68.3, 60.5, 42.5, 25.6, 17.9, 14.1, 12.9, -4.6, -5.0. $[\alpha]^{25}_D$ = –32.3 (c 1, $CHCl_3$).

2. 3. 2. Experimental Determination of Specific Heat Capacities of Dosed Reactants

As evident in Eq. (2), the knowledge of $c_{P,d}$ is becoming substantially important by increasing the temperature difference between reaction media and added material. Since TBSH **3** synthesis was performed under low-temperature conditions and on the other side the reactants were added to reaction mixture at room temperature, the precise determination of total Φ_r profile required a priori knowledge of specific heat capacities (c_P) of VMC (c_{VMC} = 1.9 mol L^{-1}) and TBSIB **4** solution in THF (mass fraction of TBSIB **4**, $w_{TBSIB\ 4}$ = 0.604), DMPU, $P(OEt)_3$, THF and saturated aqueous NH_4Cl solution.

Owning to the relatively low concentration of VMC solution it can be considered that the c_P value for VMC solution is almost equal to those one for THF, $c_{P,THF}$ = 1.71 J mol^{-1} K^{-1}.[25] Since there is no relevant literature data, the specific heat capacities of other liquids have been determined in this work using RC1 reaction calorimeter. A typical experimental procedure was as follows. The individual experiment was started by charging RC1 reactor with 600 g of liquid at room temperature. Afterwards, the liquid was stirred at rotational frequency of the stirrer, f_m = 100 min^{-1} and cooled to reach the temperature ϑ_{rm} = 17 °C. After establishing temperature steady state, the c_P was automatically determined two times by temperature ramps, ϑ_{ramp} = (17 → 20) °C and ϑ_{ramp} = (20 → 17) °C respectively. Finally, the average specific heat capacity of liquid was calculated.

2. 3. 3. Experimental Calorimetric Evaluation of TBSH 3 Synthesis

The RC1 reactor, equipped with manual dosage system and bubbler and blown with nitrogen, was initially charged at room temperature with 83.6 g of CuI (n_{CuI} = 437 mmol) and 875 mL (777.9 g) of THF. The suspension was stirred at f_m = 100 min^{-1}, inertized with nitrogen for 15 minutes and cooled to reach the temperature, ϑ_{rm} = –29 °C. After establishing temperature steady state, the U and $c_{P,rm}$ (ϑ_{ramp} = (–29 → –32) °C) were determined before adding VMC solution. The formation of divinylmagnesium cuprate (DVMCU) was initiated by the manually controlled dropwise addition (dosing volume flow rate, $q_{V,d}$ ≈ 15 mL min^{-1}) of 460 mL (450.8 g) of VMC solution (n_{VMC} = 874 mmol) under vigorous stirring (f_m = 100 min^{-1}). When VMC solution dosing was completed, the resulting dark slurry was stirred for 35 minutes. Afterwards, 110 mL (116.7 g) of DMPU (n_{DMPU} = 874 mmol) and 10 mL (8.9 g) of THF (dosing system washing) were added at ϑ_{rm} = –32 °C with $q_{V,d}$ ≈ 11 mL min^{-1}. The resulting reaction mixture was stirred for 20 minutes and then 160 mL (152,8 g) of $P(OEt)_3$ ($n_{P(OEt)3}$ = 874 mmol) and 10 mL (8.9 g) of THF (dosing system washing) were dosed at ϑ_{rm} = –35 °C in dropwise mode with $q_{V,d}$ ≈ 9 mL min^{-1}. After 30 minutes of stirring, the reaction mixture was heated to ϑ_{rm} = –29 °C and the U and $c_{P,rm}$ (ϑ_{ramp} = (–29 → –32) °C) were determined before nucleophilic substitution of TBSIB **4** with DVMCU. Thereupon, a solution of 126.5 mL (162.7 g) of TBSIB **4** ($n_{TBSIB\ 4}$ = 437 mmol) in 120 mL (106.7 g) THF was added to the reaction mixture over a period of

104 minutes ($q_{V,d} \approx 2.4$ mL min^{-1}). The stirring was continued for 30 minutes at $\vartheta_{rm} = -32$ °C and then the reductive elimination was triggered by progressive heating of reaction mixture, with the controlled heating rate, $v_{rm} = 0.45$ °C min^{-1}, to the $\vartheta_{rm} = 20$ °C. When reaction media temperature reached desired value, the stirring was continued for 30 minutes and thereupon the U and $c_{P,rm}$ ($\vartheta_{ramp} = (20 \rightarrow 17)$ °C) were determined before quenching (vinyl cuprate (VCU) hydrolysis).

The total mass of reaction mixture after TBSIB **4** solution dosing was 1869.0 g. In order to achieve optimal mixture volume during the quenching (RC1 reactor capacity limitation), 50 % of reaction mixture, which corresponds to the mass, $m_{rm} = 934.5$ g, was poured out and quenched later separately. Afterwards, the remaining mixture in RC1 reactor was cooled to reach the temperature, $\vartheta_{rm} = 0$ °C. The quenching of reaction mixture was initiated by the manually controlled addition ($q_{V,d} \approx 29$ mL min^{-1}) of 500.0 mL (535.0 g) of saturated aqueous NH_4Cl solution under vigorous stirring at $\vartheta_{rm} = 0$ °C. When NH_4Cl solution dosing was completed, the mixture was stirred at $\vartheta_{ramp} = 0$ °C for 50 minutes. Thereupon, the U and $c_{P,rm}$ ($\vartheta_{rm} = (0 \rightarrow 3)$ °C) after adding NH_4Cl solution were determined.

3. Results and Discussion

3. 1. Specific Heat Capacities of Dosed Reactants

The experimentally determined average values of specific heat capacities (c_P) of TBSIB **4** solution in THF, DMPU, $P(OEt)_3$, and saturated aqueous NH_4Cl solution in temperature range, $\vartheta = (17–20)$ °C with appurtenant standard errors, *S.E.*, and coefficients of the variation, *CV*, are collected in Table 1. The *CV* value is defined as quotient between *S.E.* and parameter's value multiplied by 100.

According to the results presented in Table 1, we ascertained that c_P values for TBSIB **4** solution, DMPU and $P(OEt)_3$ are very similar to those one for THF, whilst c_P value for saturated aqueous NH_4Cl solution is substantially higher which is in accordance with our expectations. Moreover, the comparison between *CV* values exposed that the repeatability of RC1 reaction calorimeter measurements is still within acceptable range even if reaction mass with relatively low specific heat capacity is analyzed. Consequently, in general only one experiment in RC1 reaction calorimeter is entirely enough to gain precise as well as accurate calorimetric insight into TBSH **3** synthesis.

Table 1: Numerical results derived from experimental determination of specific heat capacities of dosed reactants in TBSH **3** synthesis.

Reactant	c_P/(kJ kg^{-1} °C^{-1})[a]		*CV*/%
	Parameter's value	*S.E.*	
TBSIB **4** solution[b]	1.44	0.04	2.8
DMPU	1.53	0.03	2.0
$P(OEt)_3$	1.58	0.03	1.9
saturated NH_4Cl solution[c]	2.96	0.02	0.7

[a] temperature range, $\vartheta = (17–20)$ °C
[b] TBSIB **4** dissolved in THF ($w_{TBSIB\ 4} = 60.4\%$)
[c] NH_4Cl dissolved in water

3. 2. Reaction Enthalpies in the TBSH 3 Synthesis

Thorough calorimetric evaluation of TBSH **3** synthesis requires precise analysis of dynamic profile of heat flow due to DVMCU formation, dosing of DMPU and $P(OEt)_3$ to DVMCU solution, nucleophilic substitution of TBSIB **4** with DVMCU, reductive elimination and VCU hydrolysis separately. Thus, the ϑ_{rm} and ϑ_j, and m_{rm}, were dynamically measured during TBSH **3** synthesis and then Φ_r dynamic profile was automatically computed by Eq. (2). Once the heat flow profile was known, the overall released heats due to different above-mentioned reactions (or physical operations), were determined according to Eq. (1) by integrating the area under Φ_r profile over adequate time period using "Win RC" software. Finally, the reaction enthalpies were computed by dividing the overall released heats due to different reactions with amount of key components ($n_{CuI} = n_{TBSIB\ 4} = 437$ mmol). In addition, the corresponding adiabatic temperature rises of reaction mixture were also computed by Eq. (5).

3. 2. 1. DVMCU Formation

First reaction of the TBSH **3** synthesis (DVMCU formation) was triggered by mixing of VMC solution and CuI/THF suspension. During the manually controlled dropwise addition of 450.8 g of VMC solution to the suspension of CuI ($m_{CuI} = 83.6$ g) in THF ($m_{THF} = 777.9$ g) at $\vartheta_{rm} = -32$ °C, 11 kJ of heat was released. Thus, the reaction enthalpy of DVMCU formation was experimentally determined to be $\Delta_r H = -25$ kJ mol^{-1}. The adiabatic temperature rise of reaction mixture was calculated to be $\Delta\vartheta_{rm,ad} = 6$ °C using integrated overall released heat, $Q_r = 11$ kJ, final mass of reaction mixture, $m_{rm,f} = 1\,312.3$ g and final specific heat capacity of reaction mixture, $c_{P,rm,f} = 1.45$ kJ kg^{-1} °C^{-1}).

3. 2. 2. Dosing of DMPU and $P(OEt)_3$ to DVMCU Solution

When DVMCU formation was completed, the DMPU ($m_{DMPU} = 116.7$ g) and $P(OEt)_3$ ($m_{DMPU} = 152.8$ g) were added to reaction mixture ($m_{rm} = 1\,312.3$ g) over manual dosage system with dosing volume flow rate, $q_{V,d} \approx 11$ mL min^{-1} and $q_{V,d} \approx 9$ mL min^{-1} respectively. After each dosing completed, the dosage system was rinsed

with THF (Σm_{THF} = 17.8 g). The calorimetric study showed that released heat flows due to DMPU and $P(OEt)_3$ addition to DVMCU solution are not fully dosed controlled since there was observed thermal accumulation. Namely, in both cases approximately 80 % of overall produced heat was released during dosing. Remain fraction (20 %) of heat was produced within next 20 minutes (DMPU addition) and 30 minutes ($P(OEt)_3$ addition) respectively after dosing was completed.

The overall heats generated by the mixing of DMPU and $P(OEt)_3$ with DVMCU solution were determined to be Q_r = 21 kJ and Q_r = 7 kJ respectively. Consequently, the reaction (mixing) enthalpies and corresponding adiabatic temperature rises of reaction mixture were calculated to be $\Delta_r H$ = –48 kJ mol^{-1} and $\Delta\vartheta_{rm,ad}$ = 10 °C for DMPU addition and $\Delta_r H$ = –16 kJ mol^{-1} and $\Delta\vartheta_{rm,ad}$ = 3 °C for $P(OEt)_3$ addition. Relatively low adiabatic temperature rises expose that dosing of DMPU and $P(OEt)_3$ to DVMCU solution as well as DVMCU formation could be treated from process safety perspective as less severe exothermal events compared to other ones in the TBSH **3** synthesis.

3. 2. 3. Nucleophilic Substitution of TBSIB 4 with DVMCU

Main reaction of the TBSH **3** synthesis (nucleophilic substitution of TBSIB **4** with DVMCU) was carried out by charging 269.4 g of solution of TBSIB **4** in THF to reaction mixture (m_{rm} = 1 599.6 g). The measured (ϑ_{rm}, ϑ_j and m_{rm}) and calculated dynamic profiles (Φ_r) during this exothermic event are shown in Figure 2.

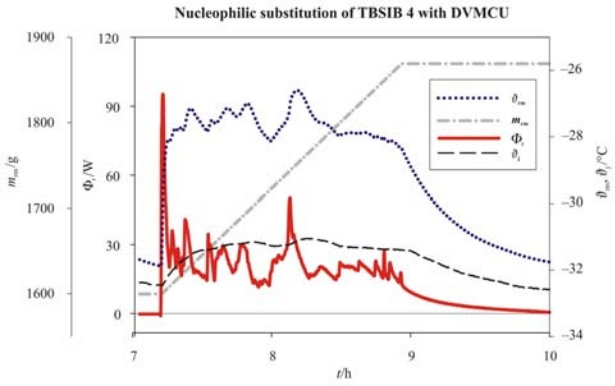


Figure 2: Measured values of ϑ_{rm}, ϑ_j and m_{rm} and calculated value of Φ_r versus reaction time during nucleophilic substitution of TBSIB **4** with DVMCU.

The integration of area under dynamic Φ_r profile exposed very strong exothermic behavior of nucleophilic substitution of TBSIB **4** with DVMCU. Namely, approximately 169 kJ of heat was released due to charging of solution of TBSIB **4** in THF to reaction mixture. Thus, the reaction enthalpy of nucleophilic addition of DVMCU on TBSIB **4** was experimentally determined to be $\Delta_r H$ = –387 kJ mol^{-1}, resulting in an adiabatic temperature rise, $\Delta\vartheta_{rm,ad}$ = 58 °C. According to relatively high exothermic potential expressed in the highest $\Delta\vartheta_{rm,ad}$ value, the nucleophilic substitution of TBSIB **4** with DVMCU has been recognized among others reactions and physical operations in the TBSH **3** synthesis as the most severe from process safety perspective.

3. 2. 4. Reductive Elimination

The presumed reductive elimination, which is associated with suggested fragmentation of trialkylcopper (III) complex and gives cross-coupling product **3,** was triggered by progressive heating of reaction mixture, with the controlled heating rate, v_{rm}= 0.45 °C min^{-1}, from ϑ_{rm} = –32 °C to the ϑ_{rm} = 20 °C. The measured (ϑ_{rm}, ϑ_j and m_{rm}) and calculated dynamic profiles (Φ_r) during this process operation are shown in Figure 3.

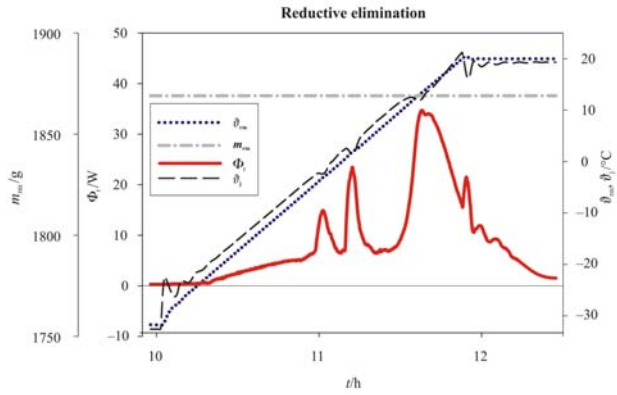


Figure 3: Measured values of ϑ_{rm}, ϑ_j and m_{rm} and calculated value of Φ_r versus reaction time during progressive heating of reaction mixture, with the controlled heating rate, v_{rm}= 0.45 °C min^{-1}, from ϑ_{rm} = –32 °C to the ϑ_{rm} = 20 °C.

As a consequence of progressive heating we observed a spontaneous highly exothermic event that consists of three distinct expressive consecutive events which are manifested as pronounced peaks as shown in Figure 3. The overall heat generated during formation of cross-coupling product **3** was determined to be Q_r = 70 kJ. Consequently, the reaction enthalpy of TBSH **3** formation and corresponding adiabatic temperature rise of reaction mixture were calculated to be $\Delta_r H$ = –160 kJ mol^{-1} and $\Delta\vartheta_{rm,ad}$ = 22 °C. This previously unknown highly exothermic phenomenon is surprising since all expected and known highly exothermic events should be associated with attack of organocuprate on alkyl halide or hydrolysis of Grignard reagent or organocuprate.[26] Furthermore, this observation is of paramount importance for the safe large scale opera-

tion. Namely, the observed overall highly exothermic three-step event takes place in organic media (THF solvent) with low specific heat capacity of reaction mixture, $c_{P,rm}$, at elevated temperature of reaction mixture (ϑ_{rm} > –10 °C). This present significant risk for an uncontrolled ϑ_{rm} increase as a function of time in the case of loss of heat exchange (cooling failure) during above-mentioned exothermic event, which is also referred to as a runaway reaction, and can lead to an explosion. In a runaway scenario a higher ϑ_{rm} which is closer to the temperature of the beginning of decomposition runway, $\vartheta_{dec,0}$ and low $c_{P,rm}$ would suggest that thermal process risks related to the observed unexpected exothermic event is much higher. Namely, if cooling system fails, the time to maximum decomposition rate under adiabatic conditions, $t_{MR,dec,ad}$ (i.e., the time between cooling failure and thermal explosion in which safety measures must be taken),[27] would be shorter at ϑ_{rm} = –10 °C (beginning of reductive elimination event) than when operating at ϑ_{rm} = (–40–(–30)) °C (DVMCU formation and nucleophilic substitution of TBSIB **4** with DVMCU) or during the quenching of the final reaction mixture with water solution which has high specific heat capacity.

The awareness and understanding of above-mentioned facts is extremely important since there is still another reactive non hydrolyzed organocopper species (RCu) present in the mixture at this point of reaction which is also not stable in its nature and would probably not sustain increased temperature caused by uncontrolled temperature rise of the previous exothermic event. In addition, its hydrolysis (bonds dissociation) is also exothermic which would lead to another adiabatic temperature rise of reaction mixture and higher probability of thermal runaway.

3. 2. 5. VCU Hydrolysis

The quenching of reaction mixture (VCU hydrolysis) was also calorimetrically investigated using reaction calorimeter RC1. The saturated aqueous NH_4Cl solution (m_{NH4Cl} = 535.0 g) was charged under vigorous stirring at ϑ_{rm} = 0 °C to crude reaction mixture (m_{rm} = 934.5 g). Briefly, the overall heat generated by this process operation was determined to be Q_r = 68 kJ. Since only 50 % of total reaction mixture was quenched, which corresponds to initial amounts of key components (n_{CuI} = $n_{TBSIB\ 4}$ = 218.5 mmol), the reaction enthalpy of VCU hydrolysis was calculated to be $\Delta_r H$ = –311 kJ mol^{-1}, resulting in an adiabatic temperature rise of reaction mixture, $\Delta\vartheta_{rm,ad}$ = 19 °C.

It has been observed, that the maximum heat flow due to VCU hydrolysis is approximately $\Phi_{r,max}$ = 0.2 kJ s^{-1}. This relatively high value of $\Phi_{r,max}$ would challenge the design of cooling capacity of the industrial reactor system especially if we want to maintain constant temperature of reaction mixture throughout quenching. Fortunately, the released heat flow due to reaction is totally dose controlled. Thus, $\Phi_{r,max}$ could be simply reduced by decreasing dosing volume flow rate of saturated aqueous NH_4Cl solution.

Summarily, the review of reaction enthalpies $\Delta_r H$, together with corresponding adiabatic temperature rises of reaction mixture, $\Delta\vartheta_{rm,ad}$, for all exothermic events that occurred in the TBSH **3** synthesis is presented in Table 2.

Table 2: Comparison of reaction enthalpies $\Delta_r H$ and corresponding adiabatic temperature rises

Reaction/physical transformation	$\Delta_r H$/ kJ mol^{-1}	$\Delta\vartheta_{rm,ad}$/°C
DVMCU formation	–25	6
Dosing of DMPU to DVMCU solution	–48	10
Dosing of $P(OEt)_3$ to DVMCU solution	–16	3
Nucleophilic substitution of TBSIB **4** with DVMCU	–387	58
Reductive elimination	–160	22
VCU hydrolysis	–311	19

It is evident from Table 2 that the previously unknown surprising highly exothermic phenomenon (ascribed to presumed reductive elimination) has almost the same thermal potential as VCU hydrolysis. In addition, it can be observed that the relative difference between reaction enthalpies of nucleophilic substitution of DVMCU on TBSIB **4** and VCU hydrolysis is less than 25 %. On the other side, the relative difference between estimated corresponding adiabatic temperature rises of reaction mixtures is more than 200 %. Therefore, it can be certainly established that in spite of similar values of reaction enthalpies the severities of those exothermic reactions are markedly different.

4. Conclusion

We have conducted the first calorimetric study of coupling between organocuprate, derived from Grignard reagent (vinylmagnesium chloride), and alky halide which was in our case (*S*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-4-iodobutanoate (TBSIB) **4**. Reaction enthalpies and corresponding adiabatic temperature rises of reaction mixture were determined for all exothermic events that occurred during the synthetic sequence with highly sensitive intermediates. Unexpected surprising spontaneous three-step exothermal event has been observed in the final stage of the process at temperature of reaction mixture, ϑ_{rm} > –10 °C, which can be ascribed to the presumed reductive elimination reaction which is associated with suggested fragmentation of trialkylcopper (III) complex and formation of the desired product and organocopper derivative (RCu). This event is followed by the final exothermal event associated with hydrolysis of remained organocopper reagent species (RCu) when the remained mixture is

quenched with saturated aqueous NH_4Cl solution. This calorimetric study gives the evidence that coupling between organocuprate and alkyl halide is not a simple S_N2 substitution reaction. In order to get better understanding of observed surprising exothermic event in coupling between organocuprate and alkyl halides, our further efforts will be placed into calorimetric kinetics studies as well as determination of optimal values of key control process parameters of these reactions which are crucially important for prevention of thermal runaway reaction accidents.

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Povzetek

Predstavljena je prva kalorimetrična študija reakcije med organobakrovim prekurzorjem, pripravljenim iz vinilmagnezijevega klorida, in primarnim alkilhalidom ((*S*)-etil 3-(*terc*-butildimetilsilil)-4-iodobutanoatom). Reakcija omogoča učinkovito pripravo (*R*)-etil 3-(*terc*-butildimetilsilil)heks-5-enoata, ki je ključni gradnik laktonzirane statinske stranske verige. Rezultati pridobljeni s kalorimetrično študijo omogočajo poglobljeno razumevanje te kompleksne nizko-temperaturne sinteze kot tudi novo razumevanje predpostavljene reduktivne eliminacije končnega intermediata v reakcijskem zaporedju. Opažen je bil presenetljiv nepričakovan spontan tri-stopenjski eksotermni pojav med kontroliranim postopnim segrevanjem zmesi končnega intermediata v reakcijskem mediju na sobno temperaturo. Ta pojav potrjuje dejstvo, da reakcija med primarnimi alkilhalidi in vinilnimi organobakrovimi reagenti ni enostavna S_N2 substitucija. Opravljena študija podaja, med drugim, tudi vrednosti reakcijskih entalpij in odgovarjajočih adiabatnih temperaturnih dvigov reakcijske zmesi za vse eksotermne pojave, ki so se zgodili med sintezo (*R*)-etil 3-(*terc*-butildimetilsilil)heks-5-enoata. Pridobljeni rezultati nam omogočajo razširitev znanja o procesih z intenzivnim sproščanjem toplote, ki ga lahko uspešno uporabimo pri varnem načrtovanju povečav tehnoloških procesov v organski sintezi in projektiranju reaktorskih sistemov z zadostno hladilno kapaciteto pri industrijski proizvodnji (*R*)-etil 3-(*terc*-butildimetilsilil)heks-5-enoata. Nadalje, rezultati študije lahko dajo osnovne smernice za podobne reakcije med organobakrovimi prekurzorji pripravljenimi iz Grignardovih reagentov in alkilhalidi.