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Safety Assessment for the Scale-up of an Oxime Reduction with Melted Sodium in Standard Pilot-Plant Equipment

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Supporting Information

ABSTRACT: A pilot-plant process is described for the reduction of 2-allyl cyclohexanone oxime with melted sodium in xylenes, toluene, and 4-methyl-2-pentanol. The *trans*/*cis* ratio was 3−4:1. Safety data are presented from a range of thermokinetic experiments (heat flow calorimetry, differential scanning calorimetry, and accelerating rate calorimetry). The process has been designed and developed to enable an expedient and safe scale-up in a standard enameled 100-L steel reactor and has been reproduced six times on 209 mol scale (each 4.8 kg sodium). Crystallization of the product 2-allyl cyclohexylamine with oxalic acid from the reaction mixture in *tert*-butyl methyl ether successfully avoided the yield losses associated with the isolation of the volatile free 2-allyl cyclohexylamine.

INTRODUCTION

trans-2-Allyl cyclohexylamine, *trans*-**3**, was an intermediate for the synthesis of an active pharmaceutical ingredient (API) at Pfizer (Scheme 1). Multikilogram quantities were required. The initial synthesis relying on Medicinal Chemistry protocols started with the oxime formation with 2-allyl cyclohexanone **1**. Reduction of the oxime **2** was performed by treatment with sodium in ethanol, affording 2-allyl cyclohexyl amine **3** that was isolated by stripping to dryness prior further derivatization.[1a] The use of elemental sodium on pilot-plant scale mandates stringent safety control. Herein, the design and safe scale-up of a sodium reduction of the 2-allyl cyclohexanone oxime **2** on multikilogram scale is described.

We first tried to circumvent the use of elemental sodium for the reduction of this α-substituted cyclohexanone oxime. According to literature—and underlined by experimental data gathered at Pfizer—generation of equatorial (*trans*) alcohols from hindered *cyclohexanones* often required the use of sodium[2−4] or other alkali metals,[5,6] while metal hydrides[7,8] or hydrogenation[9] gave mainly the axial (*cis*) product. Hutchins et al. showed[10] that the introduction of a phosphinyl imine can greatly improve the stereoselectivity in favor of the *trans* product, using tri-*sec*-butylborohydride. More recently, DeNinno et al.[1b] used lithium in anhydrous ammonia at −78 °C to afford the amine **3** with a *trans*/*cis* ratio of 10:1 in 67% yield. In addition, SiGNa Chemistry, Inc. disclosed the use of encapsulated sodium/potassium alloys in silica gel (Na−SG); these are free-flowing solids without the dangers associated with the handling of alkali metals.[11] To cope with stringent timelines for the delivery of *trans*-**3**, considering the lack of efficient alternatives, we aimed at studying the sodium reduction in more detail to render it safe for the intended pilot-plant scale.

Bänziger et al. described a Birch/Bouveault Blanc reduction using kg amounts of sodium. Precut pieces (2 cm cubes) of sodium (5.8 kg) were added to a solution of the substrate in *n*-butanol over 7 h.[12] As a measure to avoid the open exposure to a hydrogen emitting flammable fluid, the addition took place through a nitrogen-inertized double air-lock system.

For the oxime reduction discussed in this paper, the initial procedure as given in Scheme 1 used 13.5 equiv sodium that was added to a refluxing solution of the oxime **2** in 64 equiv ethanol. As also indicated above, a number of critical issues were eminent: (i) solid sodium addition to refluxing ethanol, (ii) large excess of sodium and ethanol and the associated large amounts of hydrogen gas released, (iii) control of diastereoselectivity (*cis*/*trans*), and (iv) volatile and unstable 2-allyl cyclohexyl amine **3**. We envisioned a procedure focusing on the following goals. First, sodium should be charged into the empty vessel (or to a nonreactive solvent such as xylenes), and the excess should be minimized. Second, the three substeps, i.e. generation of granulated or melted sodium, the reduction of the oxime, and the quench of excess sodium, should be fully controlled by dosage. Both the generation of heat and hydrogen were to be controlled by dosage.

RESULTS AND DISCUSSION

Initial Model Runs with Cyclohexanone Oxime. Scheme 2 outlines a simplified reaction mechanism of the sodium-mediated oxime reduction.[13] Potential radical intermediates are not shown. Mechanistically, a minimum of 4 equiv of sodium and 3 equiv of protons delivered from an alcohol are necessary for complete conversion.

We wanted first to optimize the reproducible production of a sodium sand (also named melted or granulated sodium, molecular sodium, or powdered sodium) in xylenes[13,14] and to find a safe way for the reduction of the oxime and the alcoholysis of the sodium. Dosage of solid sodium into a reacting alcohol atmosphere was excluded due to equipment limitations. We envisioned mass transfer issues associated with the stirring of the granulated or melted sodium, such as sedimentation, stirring, and gas evolution. To study both the

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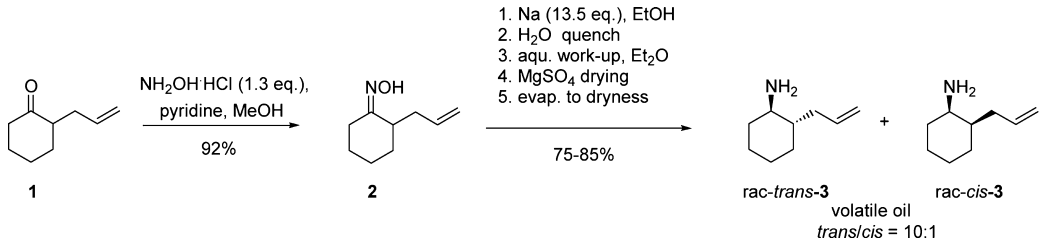
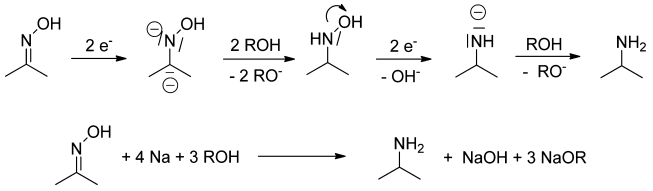
Scheme 1. Protocol as used by Medicinal Chemistry



Scheme 2. Simplified mechanism of oxime reduction by sodium in alcohols[13]



stability of the thus formed melted sodium and the hydrogen evolution, various alcohols have been added at reflux (Table 1).

Table 1. Alcohols as additives for the reduction with melted Na

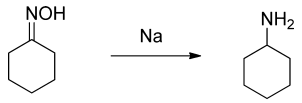
alcohol	bp (°C)
ethanol	78
isopropanol	82
cyclohexanol	160−161
2-methylcyclohexanol *cis*/*trans* mixture	163−167
4-methyl-2-pentanol	132

Solvents with a higher boiling point than that of ethanol were desirable in order to be above the melting point of sodium. Boiling point and cost triggered the choice of 4-methyl-2-pentanol (4M2P) from the selection of potential alcohols. The stability of sodium in various alcohols was also briefly discussed by Sugden and Patel,[15] and further details on the stability in *n*-butanol were given by Bänziger et al.[12]

A first familiarization experiment to generate granulated sodium by cooling melted sodium in xylenes below its melting point while stirring ended up with a broken glass impeller stirrer at 750 rpm. A second experiment—without stirring during cooling—led to sodium plates, which tended to aggregate upon restart of stirring. Therefore, all further experiments were carried out above 100 °C (sodium mp 98 °C) and at approximately 250−500 rpm, avoiding such problems by handling only liquid sodium. No stirring was applied during the melting of sodium. A related behavior was reported for sodium in *n*-butanol: at temperatures below 100 °C, sodium butoxide formation outweighed the desired reduction.[12]

For familiarization with oxime reduction, we used cyclohexanone oxime (**4**) as model substrate (Table 2). Entry 1 is based on our envisioned ideal conditions, i.e. melting of sodium in inert xylenes and dosage of the oxime **4** in equimolar 4M2P. However, to our surprise, this did not look promising: 0% conversion was observed which was likely due to poor solubility in the solvent mixture. Therefore, the following two experiments used protocols more closely related to the original procedure, i.e. addition of solid sodium to the reaction mixture. Except for entry 2 all runs were not worked up after cooling to room temperature as only the conversion was studied. Entry 2 basically reproduced the original procedure using the model substance cyclohexanone oxime **4**. The low yield of 35% was probably caused by the high volatility of cyclohexyl amine **5** (bp 134 °C). In entry 3, ethanol was replaced by the higher boiling 4M2P to check its performance giving a conversion >90%. With entry 4 we simulated a safe charge of sodium to the empty reactor by using a solution of sodium in 4M2P prior to the inverse addition of a solution of the oxime **4** in 4M2P: 91% conversion was obtained. The main drawback was the dissolution of sodium in a large excess of 4M2P (64 equiv, as in the original procedure) which would likely lead to almost quantitative formation of the corresponding alkoxide on larger scale due to the associated longer stirring times. Hence, in entry 5, sodium was melted in xylenes without stirring followed by the addition (with stirring) of the oxime **4** in 64 equiv of 4M2P (main difference as compared to entry 1). This led to 98% conversion. Additional ethanol was added to ensure that excess

Table 2. Familiarization runs using cyclohexanone oxime 4 as model substrate[a]



4 **5**

entry	alcohol	xylenes	procedure	conversion[b] (%)
1[c]	4M2P 6 equiv	10.5 vol	dose **4** in 4 equiv 4M2P to Na in xylenes at 105 °C; dose 2 equiv 4M2P	0
2[d]	EtOH 64 equiv	none	add Na to **4** in 37 equiv EtOH at 80 °C; dose 27 equiv EtOH; heating to 110 °C	99
3	4M2P 64 equiv	none	add Na to **4** in 37 equiv 4M2P at 110 °C; dose 27 equiv 4M2P; heating to 156 °C	92
4	4M2P 64 equiv	none	dose **4** in 27 equiv 4M2P to Na in 37 equiv 4M2P at 115 °C; heat to 156 °C; hold for 1 h 45 min	91
5	4M2P 64 equiv EtOH 43 equiv	9 vol	dose **4** in 64 equiv 4M2P to Na in xylenes at 121 °C; dose 27 equiv EtOH; hold for 1 h; dose 16 equiv EtOH; hold for 39 min	98

[a]All runs used 13.5 equiv Na, except for entry 1 which was performed with 6 equiv Na. Scale: 16 (entries 4, 5) and 32 mmol **4** (entries 2, 3). [b]Conversion as determined by GC. [c]RC1 experiment, 167 mmol **4**. [d]Isolated yield 35%.

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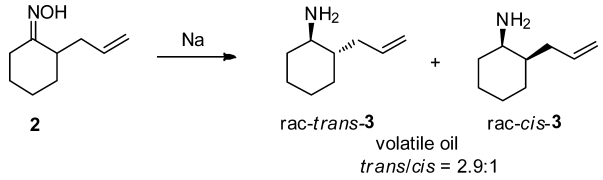
Table 3. Initial process development with 2-allyl cyclohexanone oxime 2[a]



entry	alcohol	xylenes	procedure	IPC: purity (%) trans/cis[b]	yield (%) trans/cis[c]
1	as entry 5, Table 2	9 vol	dose **2** in 64 equiv 4M2P to Na in xylenes at 121 °C; dose 27 equiv EtOH; dose 16 equiv EtOH	>90 3.0:1.0	62 4.3:1.0
2	EtOH 128 equiv	–	based on Medicinal Chemistry protocol (Scheme 1)	>45 2.9:1.0	72 5.9:1
3	EtOH 64 equiv	9 vol	dose **2** in xylenes to Na in xylenes at 121 °C; dose 64 equiv EtOH	>90 2.9:1.0	54 4.5:1.0
	EtOH 43 equiv		dose 43 equiv EtOH		

[a]All runs used 16.1 mmol **2** and 13.5 equiv Na. [b]Conversion and *trans*/*cis* ratio in IPC sample after approximately 1 h as determined by GC. Conversions of 87–99% were detected. Sample preparation: 0.5 mL of the reaction mixture (waxy solid after cooling) was quenched with 0.5 mL water and extracted with 1 mL MTBE (methyl *tert*-butyl ether). The organic phase was analyzed by GC (% a/a). [c]Isolated yield of crude product; *trans*/*cis* ratio as determined by GC.

Table 4. Process development with reaction calorimetry (RC1)[a]

entry	Na (equiv)	alcohol	xylenes	procedure	conv.[b] (%)	$(Q_r/m_r)_{max}$[c]
1	13.5	4M2P 63.8 equiv	9 vol	dose **2** in 64 equiv 4M2P to Na in xylenes at 121 °C over 120 min; hold 40 min	72	−233 during dosage: after 13 equiv 4M2P dosed
2	13.5	4M2P 10 equiv	9 vol	dose **2** in 10 equiv 4M2P to Na in xylenes at 120 °C over 47 min	99	−206 30 min after end of dosage
		EtOH 20 equiv		hold 14 h; dose 20 equiv EtOH over 77 min		
3	6.0	4M2P 5 equiv	11 vol	dose **2** in 5 equiv 4M2P to Na in xylenes at 120 °C in 3 portions (each over 10 min and 1 h waiting time)	68	−150 at the end of the EtOH quench
		EtOH 5 equiv		dose 5 equiv EtOH over 30 min		
4	6.0	4M2P 5 equiv	9 vol	dose **2** in 5 equiv 4M2P to Na in xylenes at 120 °C over 30 min	96	−123 4 h after dosage
				hold 14 h		
5	10.0	4M2P 9 equiv	9 vol	dose **2** in 9 equiv 4M2P to Na in xylenes at 120 °C over 31 min	94	−247 45 min after dosage
				hold 27 h; add water at 90 °C		
6	10.0	4M2P 2 equiv	9 vol	dose 2 equiv 4M2P to Na in xylenes at 120 °C hold 36 min	98	−204 during dosage of **2**
		4M2P 9 equiv		dose **2** in 7 equiv 4M2P at 120 °C over 31 min		
				hold 21 h, dose 2 equiv 4M2P, add water at 90 °C		
7[d]	10.0	4M2P 2 equiv	4.5 vol + 4.5 vol toluene	dose 2 equiv 4M2P to Na in xylenes/toluene at 120 °C	70	reflux mode without calibration
		4M2P 9 equiv		dose **2** in 7 equiv 4M2P over 62 min		
				hold 1.25 h dose 2 equiv 4M2P add water at 90 °C		

[a]Entries 1–6 used 64.5 mmol **2**. Crude **3** was isolated in >90% a/a purity by GC. [b]Conversion as determined by GC. Sample preparation: 0.5 mL of the reaction mixture (waxy solid after cooling) was quenched with 0.5 mL water and extracted with 1 mL MTBE. The organic phase was analyzed by GC (% a/a). [c]Maximum heat flow (W/kg m_r) without Q_{dos} term. [d]193.5 mmol **2**.

sodium was destroyed. With this procedure, a safe handling of sodium on scale seemed possible. However, the high dilution would result in a very low volume throughput. As this last familiarization run (entry 5) gave promising results, further experiments were continued with the 2-allyl cyclohexanone oxime **2** (Table 3).

Process Development of the Oxime Reduction. The first experiment with 2-allyl cyclohexanone oxime **2** (Table 3, entry 1) was run under the conditions previously defined in Table 2, entry 5. Conversion and purity levels greater than 90% were obtained. However, the *trans*/*cis* ratio was only 3:1 in the In-Process-Control (IPC) by GC compared to the 10:1 value reported in the Medicinal Chemistry protocol. Repetition of the original Medicinal Chemistry procedure in ethanol (entry 2) with **2** revealed that in our hands a ratio of only 2.9:1 was obtained in the reaction mixture. However, it was shown for all three runs that the *trans* isomer was enriched up to a ratio of 5.9:1 upon workup according to the original procedure.[16] Run 3 was carried out to check if the potential dimerization (via ketyl radicals)—a conceivable side reaction prior to reprotonation—took place, by allowing a 75 min aging period after addition of the oxime **2** in xylenes and before the addition of ethanol. No dimerization was detected by GC.

Further Development and Hazard Evaluation Using Reaction Calorimetry. For practical reasons, further experiments were carried out in the RC1 with heat flow and gas generation rate in our focus (Table 4). It is noteworthy that the heat flow trace is, in general, calculated without the Q_{dos} term which is quite large due to a dosage of a solution of 20 °C to a reaction mixture at 120 °C. For this evaluation we did not distinguish between the desired reaction (the reduction of the oxime **2** with sodium and alcohol) and the inevitable alcoholysis of sodium. Interestingly, a large heat flow is always accompanied by a large hydrogen flow despite the fact that only the alcoholysis of the sodium should lead to hydrogen generation based on the assumed reaction mechanism.

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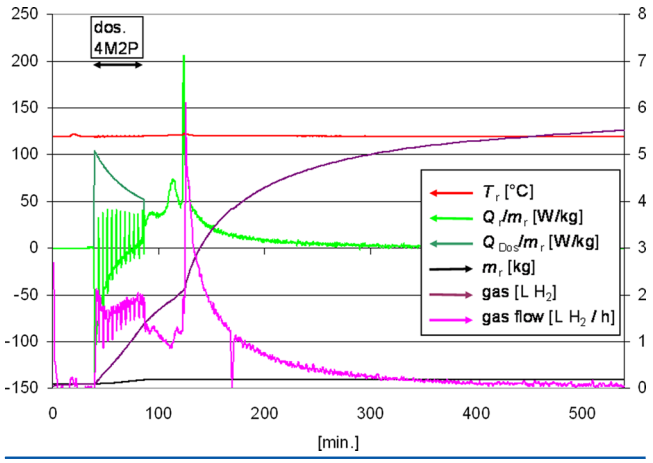
In a separate experiment, the stability of sodium in 4M2P was studied: 0.033 mol of 4M2P was added during 10 min to 1 mol of sodium in 200 mL xylenes at 105 °C, whereby a reaction power of −40 W/kg reaction mixture (m_r) and a dosage-controlled gas evolution were measured, corresponding to the expected amount of 0.39 L H_2. However, this side reaction may be influenced by the solvent composition (polarity) and temperature.[12]

Upon scaling up by a factor of 4 (Table 4, entry 1), the longer dosage time (120 min) led to a lower conversion due to the expected consumption of sodium by alkoxide formation. This effect was also promoted by the large excess of alcohol (64 equiv), thus reducing volume productivity substantially. It is also assumed that more product was lost during workup due to the high dilution (isolated yield 62%). The mass of the dosed 2-allyl cyclohexanone oxime **2** and 4M2P solution was very high as compared to the initial mass (xylenes and sodium). Dosage started when the sodium was present as large droplets in xylenes. At this point, the sodium droplet size changed frequently. Small-sized sodium droplets seemed to result in higher exothermic heat flow than those of larger size (low surface area). At the end of the dosage, the sodium was completely consumed, and gas evolution ceased. No additional alcohol was necessary to destroy excess sodium.

In entry 2, the excess of 4M2P was reduced from 64 to 10 equiv. The goal was to implement a procedure with stoichiometric amounts of sodium and 4M2P. The RC1 data for this run are depicted in Chart 1. During the tremendous heat flow after

Chart 1. RC1 plot of entry 2, Table 4

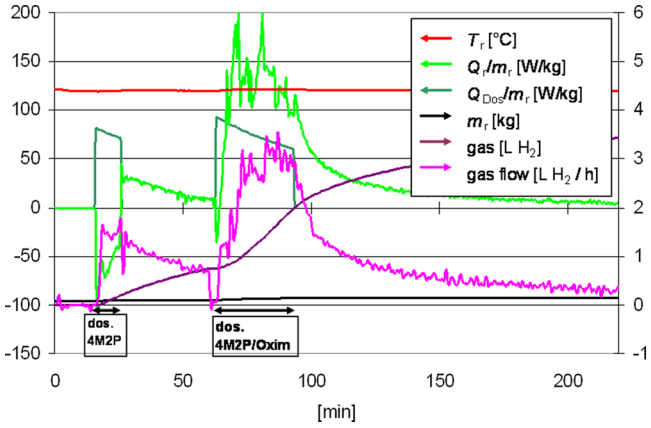


completion of the dosage of the solution of the starting material, small sodium droplets were observed. When the heat flow dropped down, again large sodium droplets were observed. The process is highly controlled by the sodium surface area. The surface area is a function of stirrer speed, baffles, stirrer type, solvent density, polarity, and surface tension (it is easier to generate fine droplets in apolar xylenes than in more polar mixtures of 4M2P, sodium, and **2**).

The following experiments focused on the accumulation as the remaining safety issue. First, the solution of the oxime **2** in 4M2P and xylenes was added in three portions, each with at least 1 h reaction time after the end of dosage (entry 3). In addition, the equivalents of sodium and 4M2P were lowered to 6 equiv and 5 equiv, respectively, as mechanistically a minimum of 4 equiv of sodium and 3 equiv of alcohol are necessary (see Scheme 2). After completion of the reaction, most of the sodium should be consumed. The remaining sodium was dissolved by adding a mixture of ethanol and 4M2P. This approach was not further evaluated due to the low conversion. In entry 4, in contrast to the procedure in entry 3, the solution of **2** in 4M2P and xylenes was added in one portion within 31 min (equivalents were kept unchanged). As observed in previous experiments (e.g., entry 2), a delayed exothermic effect was measured. In entry 5, the equivalents of sodium were lowered to 10 equiv as compared to entry 2 while keeping the equivalents of 4M2P at 9 equiv. Heat release was again delayed and reached a maximum heat flow of −247 W/kg, 43 min after the end of dosage. The accumulation of the process had to be further minimized for a scale-up into the pilot plant.

In entry 6, 2 equiv of 4M2P was added prior to the addition of the oxime **2** with the aim of mitigating the delayed exotherm. This was based on the hint from entry 1 that large excess of alcohol led to less accumulation (exotherm during dosage) and the experience that very low amounts of alcohol led to delayed exotherms. The increase of polarity of the reaction mixture was beneficial. The thermal safety of this process was improved (Chart 2).

Chart 2. RC1 plot of entry 6, Table 4



The following enthalpies consider the Q_{dos} term. However, the accuracy is reduced by the small starting volume, the still ongoing alcoholysis after the dosage of 4M2P, and the ongoing alcoholysis even 10 h after the dosage of the oxime/4M2P solution. For the temperature range of 20−120 °C an average C_p value of 3200 J/(kg*K) for 4M2P has been extrapolated from the value of 2670 J/(kg*K) at 20 °C. On the basis of the hydrogen release 0.75 L/0.13 mol 4M2P after 10 min of dosage and a waiting time of 36 min, only about 50% of the alcohol did react with the sodium. During the 31 min dosage of the oxime solution 62% of the heat is released (−463 kJ/kg total) with a maximum heat flow of −285 W/kg (−204 W/kg without taking Q_{dos} into account). This value is too high for heat removal by jacket cooling and therefore calls for a heat removal by reflux condenser. Hydrogen release again parallels the reaction enthalpy. Two hours after the end of dosage about one-third of the 10 equiv sodium is converted into hydrogen. In case of a power failure, taking into account an enthalpy of evaporation for xylene of −354 kJ/kg, the 38% heat accumulated would lead to an evaporation of about 40% of the xylene without recondensation.

To reduce the boiling point of the reaction mixture for a process under reflux conditions, a 1:1 w/w mixture of toluene/xylenes was proposed in order to have a solvent mixture with a boiling point of approximately 120 °C (entry 7). A further driving force to reduce the process temperature was the fact that the boiling point of pure xylenes is too close to the onset of **2**

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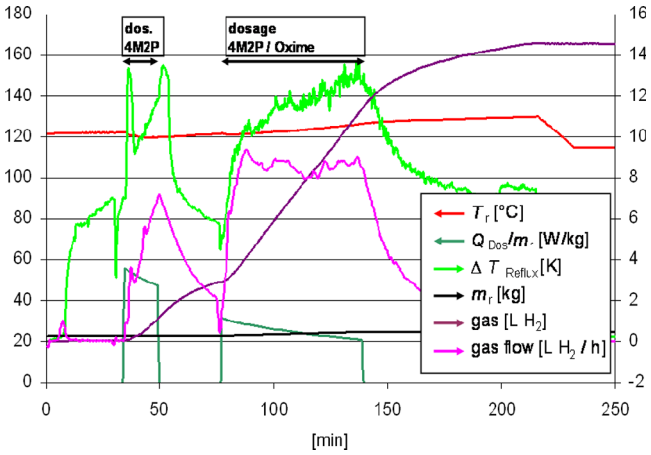
according to DSC and ARC. The size of the sodium droplets in xylenes was very small (approximately 1 mm). The addition of 4M2P resulted in an agglomeration of sodium consisting of one single large drop. During dosage of the oxime **2** solution, smaller drops were formed, and their size continuously decreased and finally reached 2−3 mm in diameter at the end of the dosage. An additional 2 equiv 4M2P was necessary to dissolve the sodium completely in a reasonable time.

Finally, the aim of run in entry 7 was to reproduce entry 6 on larger scale (scale-up factor 3) including the use of toluene/xylenes as solvents. The heat balance coefficient of the reflux condenser was not calibrated. Therefore, the thermal data of the reduction (Chart 3) were only evaluated qualitatively. It is evident that the

Chart 3. RC1 plot of entry 7, Table 4



heat flow and hydrogen evolution mostly ceased after the end of the dosage. The hydrogen flow during dosage is constant.

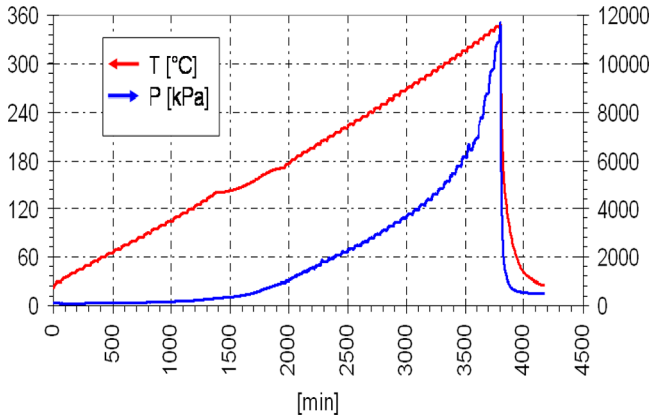
Likely, it seems possible to further reduce the equiv of sodium towards 6 equiv. However, this was not studied further. For all runs (entries 1−7, Table 4) the *trans*/*cis* ratio varied between 2.8:1 and 3.9:1 in the IPC and was only slightly increased to 2.9:1 or 4.0:1 after workup. For entries 2−7 in Table 4, the new workup described below was carried out.

Isolation and Workup. In our hands, workup following the original procedure, i.e. quench with water, acidification, and extraction with MTBE followed by adjusting the pH to 14 and extraction with MTBE, gave an organic phase containing the 2-allyl cyclohexylamine **3**. Due to the high volatility described for 2-allyl cyclohexyl amine **3** (boiling point 65 °C at 16 mbar, estimated boiling point at normal pressure approximately 170 °C) and the use of 4M2P (bp 130 °C) isolation by evaporation to an oil was not feasible. The experiments showed that 4M2P was present in up to 20% w/w in the product solution when the original procedure was used. Any residual alcohol impeded the follow-on steps that did not tolerate protic solvents. Therefore, isolation of the 2-allyl cyclohexyl amine **3** as a salt was deemed attractive (Scheme 3). A first experiment with addition of 1.0 equiv oxalic acid in MTBE to precipitate **3** from the organic phase as a salt gave 82% recovery on a 0.68 g scale. Although the oxalate precipitated readily, it was shown that the recovery after filtration was only 60% after stirring for 2 h; stirring for an additional 5 h gave another 24% and yet another 6% yield resulted after two more hours. Therefore, the following experiments always included stirring the suspension for >10 h, usually overnight. On scale, the procedure was changed to inverse addition of the amine **3** solution to a solution of oxalic acid in MTBE for practical reasons. Titration of the resulting oxalate with 0.1 N NaOH indicated that the depicted 1:1 salt **6** (Scheme 3) was present.

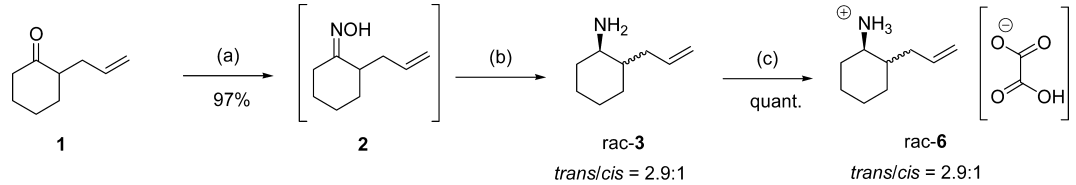
DSC Data. Due to the low onset of 2-allyl cyclohexanone oxime **2** (177 °C, see Supporting Information) the temperatures given in the experimental procedure should not be exceeded, and solutions of 2-allyl cyclohexanone oxime **2** should not be distilled to dryness. Handling its solution in MTBE was deemed safe due to the presence of a boiling barrier. Isolated 2-allyl cyclohexyl amine oxalate **6** can be considered stable up to 60 °C. However, the free amine **3** is not stable according to DSC. Still, prolonged handling under the reaction conditions at 120 °C or subsequent distillation at 80 °C had not affected the quality.

Accelerating Rate Calorimetry (ARC) Data. Self-heating was detected starting at 140 °C, and the pressure vs temperature indicated the generation of noncondensable gases (Chart 4). It is recommended to use a boiling barrier

Chart 4. ARC data of deprotonated 2-allyl cyclohexanone oxime 2



Scheme 3. Telescoped oxime formation−oxime reduction sequence as used for pilot-plant batches[a]



[a]Reagents and conditions. (a) $NH_2OH{\cdot}HCl$ (1.3 equiv), pyridine, MeOH, MTBE, solvent exchange to 4-methyl-pentanol, concentration: **2** in 7.1 vol 4-methyl-pentanol. (b) (i) Na (10 equiv), xylenes, toluene, 110 °C, (ii) 4M2P (1 equiv), 110 °C, (iii) **2** in 4-methyl-2-pentanol (7 equiv), 120 °C, (iv) 4-methyl-2-pentanol (2 equiv), 120 °C, (v) water, 32% HCl, 100 °C. (c) Oxalic acid (1.0 equiv), MTBE, 4-methyl-2-pentanol, 20 °C (97% over 3 steps).

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(xylenes/toluene 1:1 w/w, bp 120 °C) for the reduction of 2-allyl cyclohexanone oxime **2** with sodium in order to avoid undesired byproduct resulting from the thermal decomposition of 2-allyl cyclohexanone oxime **2** deprotonated by sodium alcoholate (for sample preparation see Supporting Information, ARC data). It is noteworthy that in the final process the 2-allyl cyclohexanone oxime **2** is added to sodium in the solvent mixture. So, **2** is not present as full batch like in the ARC. This allowed the reaction to run only 20 °C below the onset.

Scale-up in Pilot Plant. To ensure a safe scale-up of the procedure described above, an intermediate scale-up with 410 g sodium (5 L reaction volume) was performed in a 100-L vessel (scale-up factor 90) to test the different reactor geometry (cylindrical Büchi steel-enamel reactor with impeller stirrer and baffle located at 11.5 L, minimal stirring volume 1 L). One change with respect to the run in entry 7 (Table 4) was carried out: only 1 equiv 4M2P instead of 2 equiv 4M2P was added prior to the addition of the oxime **2** to increase the excess of sodium by 1 equiv. Possibly, this amount could be further reduced, but this was not studied anymore. A lower than expected conversion of 64% was measured after 5 h at 115 °C. The low volumes led to rather inefficient stirring (baffle with different plates not immersed), meaning that the sodium was not finely dispersed by all baffles. Upon further scale-up, a faster conversion was expected. The product was isolated in 57% yield with a purity of 67/22% a/a GC (*trans*/*cis*). Indeed, in the next intermediate scale-up run with 2.0 kg sodium (23 L reaction volume), a conversion of 91% after only 2 h at 120 °C was measured. The *trans*/*cis* ratio in IPC was 2.8:1.0. During the quench with water a thick suspension was formed. The product was isolated in 95% yield with a purity of 71/24% a/a GC (*trans*/*cis*). On the basis of these results, the remaining material was converted in six runs, each using 4.8 kg sodium (56 L reaction volume) based on the elaborated procedure (entry 7, Table 4). For details see also the Experimental Section. During the addition of water the suspension, as formed during the quench, became partly unstirrable (stirring continued at the bottom, and the upper volume remained an unstirred, gel-like mixture) during a short time of the addition, partially due to the stirrer and reactor design (impeller and large height-to-diameter ratio). This could likely be improved by quenching with a larger excess of the polar 4-methyl-2-pentanol but was not tested. After removal of 50% of the original amount of MTBE, the solution was diluted with additional MTBE and the solution stored after each run. The final oxalate salt formation was carried out with combined runs 1−3 and runs 4−6 (Scheme 3) by an inverse addition of the solution in MTBE to 1.0 equiv oxalic acid in MTBE at 20 °C. Both combined workup runs led to the expected white solid rac-**6** in quantitative yield and 71/24% a/a GC (*trans*/*cis*).

CONCLUSION

On the basis of extensive thermokinetic experiments, our goal to develop a safe procedure of the oxime reduction by melted sodium was achieved. The following features have been key in optimizing the initial protocol. (1) It was shown that the presence of 4M2P instead of ethanol was essential to avoid accumulation. (2) An inverse addition was applied, i.e. addition of 2-allyl cyclohexanone oxime **2** in 4M2P to melted sodium in xylenes/toluene instead of solid addition of sodium to refluxing ethanol. This prevented the open handling of sodium in ethanol vapors. (3) The equivalents of sodium were reduced from 13.5 equiv to 10.0 equiv, and only 10.0 instead of 64.5 equivalents of alcohol was used. This measure minimized the degradation of sodium to the alkoxide upon scale-up. (4) Xylenes/toluene were used as cosolvents to melt sodium. This solvent system generated a stirrable form of sodium during the reaction and secured a boiling barrier at 120 °C. (5) The isolation was streamlined by precipitating 2-allyl cyclohexyl amine **3** as oxalate salt **6** instead of evaporation of the volatile **3**.

In summary, a safe and practical procedure for the reduction of 2-allyl cyclohexanone oxime **2** was developed and successfully implemented on kilogram scale, using 4.8 kg sodium, to yield the corresponding amine **3** as oxalate salt **6**. The procedure was safely reproduced 6 times with 4.8 kg sodium in a 100-L reactor.

EXPERIMENTAL SECTION

General. Reported temperatures are internal temperature unless otherwise stated.

Safety Measures with Elemental Sodium. Generally, the process should only be carried out in a reactor equipped with an oil-cooled reflux condenser. Also, due to the ambiguous results of the reaction exotherm, a mixture of xylenes or toluene was placed in a feeding tank as a contingency for quick dilution of the reaction mixture in case of a sudden exotherm that would lead to uncontrolled boiling. Use a constant nitrogen purge during operations generating hydrogen gas to ensure dilution in exhaust gas. Sodium reacts with many substances very exothermically, in some cases under explosion, the given list not being complete:[17] all halogenated solvents, water, DMF, hydrazine, charcoal, sulfides, acetylenes, metal halogenides, ammonium salts, oxides, oxidants, acids, alcohols, oxygen, carbon dioxide, and chlorinated organic compounds. It is recommended to test seals and gaskets under friction if they are unavoidable, e.g. charging via a butterfly valve (in analogy to Teflon that is not stable under friction with lithium). For decontamination and fires: use only extinguisher for metals, powder extinguisher, dry sand, or in case of a spillage also sodium chloride or soda. Do not use water or carbon dioxide extinguisher.

2-Allyl Cyclohexanone Oxime (2). A dry 100-L reactor was purged with nitrogen, and the jacket temperature was set to 20 °C. $NH_2OH{\cdot}HCl$ (10.1 kg, 1.1 equiv) was loaded, followed by MeOH (95 L). Note: a solution was obtained. Pyridine (19 L, 1.7 equiv) was added at 17−18 °C over 8 min. Allyl cyclohexanone **1** (18.2 kg, 1 equiv, 131.7 mol) in MeOH (18 L) was added at 18−21 °C over 31 min. Stirring was continued at 20 °C for 1 h 17 min. IPC by GC: 100% conversion. Sat. aqueous NaCl solution (60 L) was added at 20 °C over 10 min. Note: a suspension was obtained. Aqueous 0.5 N HCl (132 L, 0.5 equiv) was dosed at 20−22 °C during 18 min. MTBE (152 L) was added, and stirring was continued at 20 °C for 5 min. After phase separation, the inorganic phase was washed with MTBE (105 L). The organic phase was washed twice with sat. NH_4Cl solution (2 × 45 L). The organic phase was washed with water (49 L). 131 L of a total of 256 L solvent was removed at jacket temperature 60 °C to afford **2** as a yellow solution in MTBE (106 L). Yield: 97%, corrected for LOD (loss on drying). Purity: 94.7% a/a (sum of isomers), LOD 81.5% w/w, off-white solid after concentration to dryness of an aliquot. NMR corresponds to reference 8.

2-Allyl Cyclohexyl Amine Oxalate (6). A dry 100-L reactor was purged with nitrogen, and the jacket temperature was set to 20 °C. 4-Allyl cyclohexanone oxime **2** (19.6 kg) in MTBE (106 L) was transferred into the reactor. Solvent (67 L) was removed at a jacket temperature of 60 °C. 4-Methyl-2-propanol

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(114 L) was added to the solution. Solvent was removed at a jacket temperature of 60 °C and p = 80 mbar until the distillation stopped. After cooling to 20 °C, the solution was stored in a barrel for the subsequent six analogous runs with sodium followed by two isolations as oxalate salt.

The reactor was rinsed with xylenes. The reactor was loaded with xylenes (12.8 L). Sodium (4.8 kg, 10.0 equiv) was loaded into the reactor. Note: sodium was kept under kerosene or xylenes. The reactor was purged with nitrogen, and toluene (13.0 L) was added. The temperature was set to 110 °C. Note: sodium is melted at jacket temperature (max) = 130 °C, no stirring was applied. The temperature was set to 120 °C. Stirring was started. 4-Methyl-2-propanol (2.6 L, 1.0 equiv) was added at >112 °C during at least 15 min. Stirring was continued for 30 min at 115−120 °C. A sixth part of the above solution of 2-allyl cyclohexanone oxime **2** (22.7 L, 1 equiv) in 4M2P (7 equiv) was added during at least 60 min at >115 °C. Note: reflux during part of the addition. Stirring was continued for 2−14 h at 120 °C. IPC by GC: 90% conversion.

4-Methyl-2-propanol (5.2 L, 2.0 equiv) was added at 120 °C during at least 4 min, and stirring continued for at least 1 h at 120 °C. The temperature was set to 90 °C. Water (23.5 L) was added at 120−100 °C during at least 30 min for first 8 L. Note: in the beginning the addition was very exothermic, and the suspension, as formed during the quench, became partly unstirrable. The two-phase mixture was cooled to 15 °C, and 32% HCl (12.5 L, 6.0 equiv) was added at 15−25 °C; pH = 11. 30% aqueous NaOH was added to readjust the pH to >13. The phases were separated. The organic phase was washed with 0.1 N NaOH (15.0 L). MTBE (45 L) was added to the organic phase. Solvent (50% of the MTBE amount added) was removed at jacket temperature 80 °C. MTBE (23 L) was added, and the solution OP 1 (approximately 70 L each) was stored after each of the six runs without further analysis.

A dry 630-L reactor was loaded with oxalic acid (5.60 kg, 1.0 equiv), and MTBE (60 L) was added. Upon stirring, a clear solution was obtained. At 20 °C OP 1 (210 L combined for three runs with sodium) was added during at least 15 min. Note: a white suspension was formed. Stirring was continued for at least 12 h at 20 °C. The suspension was filtered over a filter nutsch. The filter cake was washed with MTBE (39 L). The white solid was dried on the nutsch by a flow of N_2. Lot 1: 23.44 kg, lot 2: 17.65 kg. Yield: quant., corrected for loss on drying (LOD). Purity: 71/24% a/a (*trans*/*cis*) (identical result for both lots), LOD lot 1: 19% w/w, lot 2: 8% w/w. NMR and GC correspond to reference from Pfizer.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details on DSC and ARC data; GC method including a GC-trace of **3**; copies of ^{1}H NMR of compounds **2** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on June 19, 2012, with incorrect legends in Charts 1 and 2. The corrected version was reposted on June 21, 2012.