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Development of a Scalable Process for the Synthesis of *trans*-2-Methylcyclopropanecarboxylic Acid

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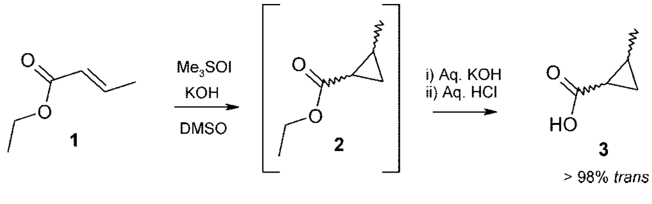
Abstract:

A scalable process has been developed for the synthesis of *trans*-2-methylcyclopropanecarboxylic acid via the stereoselective cyclopropanation of ethyl crotonate with dimethylsulfoxonium methylide (Corey's ylide). This well-known reaction is generally low yielding and very challenging to scale up as it involves highly reactive reagents. A design of experiment (DoE) allowed us to quickly define the optimal ranges for the reaction parameters. A very significant increase of the yield was obtained by adding the ylide to ethyl crotonate in DMSO at 80 °C in anhydrous conditions. In view of a scale-up at a multikilogram scale, several experiments were then performed combining Process Analytical Technologies (PAT) and Calorimetry (Dynamic DSC, Adiabatic Reaction Calorimetry and Vent Sizing Package). For safety reasons at high temperatures on large scale the reaction was also evaluated in a continuous flow reactor. Thanks to these studies, we were able to develop an efficient process avoiding the hazardous accumulation of the thermally unstable dimethylsulfoxonium methylide.

Introduction

The 2-substituted-cyclopropanecarboxylic acid pharmacophore is found in several compounds of biological importance.[1] *trans*-2-Methylcyclopropanecarboxylic acid **3** has been prepared by several synthetic methods. Among these, two approaches are typically used, namely the Simmons–Smith[2] and Corey's cyclopropanation procedures.[3] We decided to focus our attention on the latter method which is generally preferred for electron-poor olefins. Interestingly, although this reaction has been known for a long time, little has been done in terms of developing a scalable process. Cyclopropanation of *trans*-ethylcrotonate **1** is achieved by reaction with dimethylsulfoxonium methylide ("Corey's ylide"), prepared from trimethylsulfoxonium iodide or chloride and a base in solvents such as DMSO or THF at or below room temperature. We focused on the trimethylsulfoxonium iodide which is much more readily available. The majority of the literature procedures utilize sodium hydride as base. For obvious safety concerns, we decided to evaluate other bases. A first screening was performed, indicating that NaOH, KOH, or *t*ButOK in DMSO afford similar results as NaH.[4] We decided to move forward with powdered potassium or sodium hydroxide in DMSO for the first large-scale reaction aiming to support initial supply of scale-up material.[5] Although the yield was quite low, this modified procedure allowed us to rapidly deliver 1.2 kg of highly pure *trans*-2-methylcyclopropanecarboxylic acid **3**.

Scheme 1. **Cyclopropanation of *trans*-ethyl crotonate with dimethylsulfoxonium methylide**



Results and Discussion

Based on several literature protocols, the most typical way to perform the cyclopropanation reaction is to pre-form dimethylsulfoxonium methylide before slowly adding ethyl crotonate in order to control the exotherm[3,6] (Scheme 1). However, our results were surprising: the best yields (although never more than 30%) were obtained with a very fast addition (a few seconds at 5–10-g scale) of ethyl crotonate on the ylide solution in the absence of external cooling, which gave a maximum temperature of 50–55 °C. Lower yields (10–15%) and incomplete conversion of ethyl crotonate (80–85%) were obtained with the typically reported slow addition (from 5 to 15 min) of ethyl crotonate. Obviously, the fast addition procedure would not be easily scalable, but it indicates that the side reactions could be minimized in the absence of a large excess of ylide (i.e., addition of ethyl crotonate in a single

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(1) (a) Lawrence, D. S. *PCT Int. Appl. WO 07/9300*, 2005. (b) Dourtoglou, V.; Koussissi, E.; Peyritis, K. *Plant Growth Regul.* **2000**, *30*, 79.

(2) (a) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, *80*, 5323. (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.

(3) (a) Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1962**, *84*, 867. (b) Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.

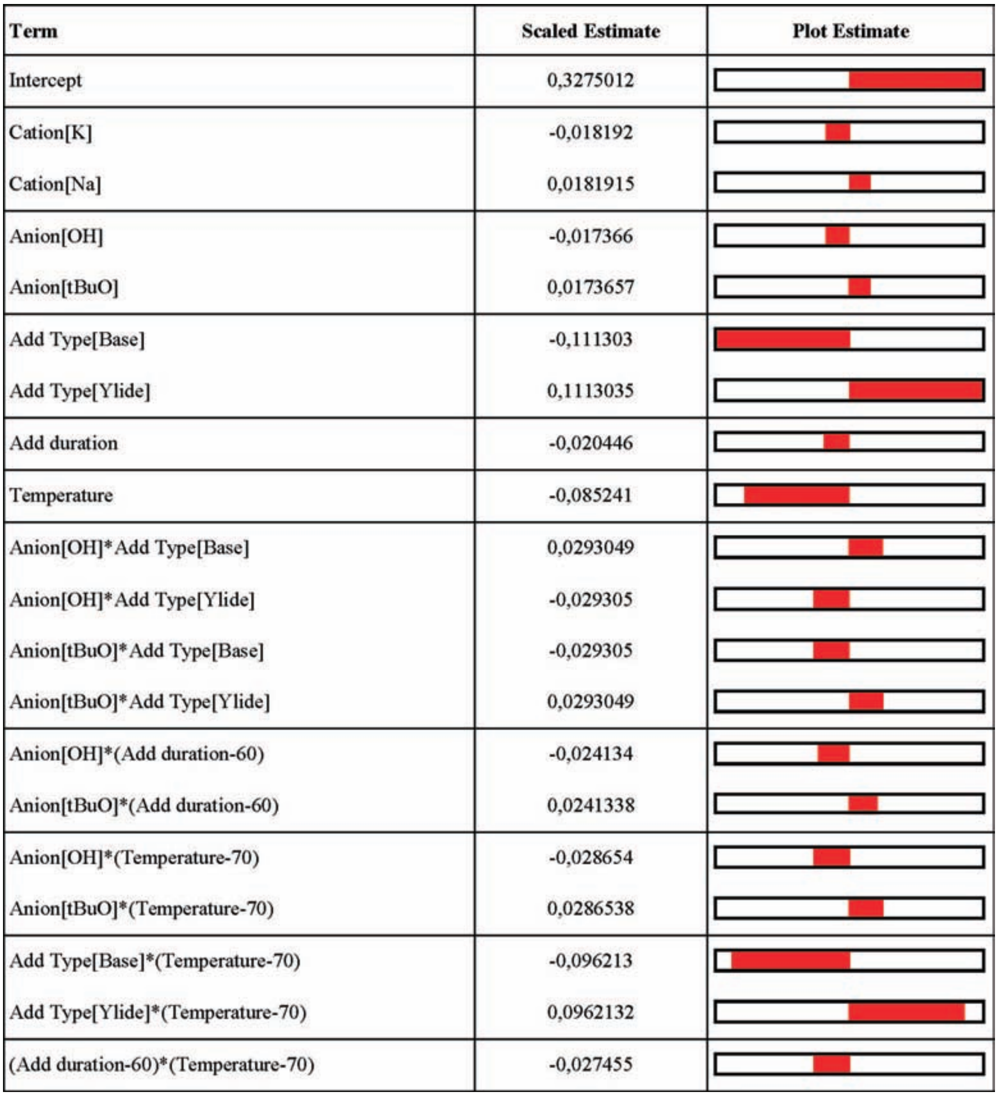
(4) DMSO was identified as preferred solvent (ca. 30% yield). *N,N*-Dimethyl-acetamide (DMAc), *N,N*-dimethylformamide (DMF), 1,1,3,3-tetramethyl-urea (TMU), 1,4-dioxane, *N*-methyl-pyrrolidin-2-one (NMP), 1,3-dimethylethylene urea (DMEU) gave comparable yields (ca. 20%). Diglyme, acetonitrile, and benzonitrile gave lower yields (ca. 15%). A summary table is included as Supporting Information.

(5) For a similar reaction using powdered NaOH in DMSO at room temperature, see: Clark, A.; Jones, E.; Larsson, U.; Minidis, A. *PCT Int. Appl.* WO 01/92200, 2001.

(6) Landor, S. R.; Punja, N. *J. Chem Soc. (C)* **1967**, *23*, 2495–2500.

10.1021/op600275g CCC: $37.00

Table 1. **First-order linear model with five interaction terms: scaled estimates**



Term	Scaled Estimate	Plot Estimate
Intercept	0,3275012	
Cation[K]	-0,018192	
Cation[Na]	0,0181915	
Anion[OH]	-0,017366	
Anion[tBuO]	0,0173657	
Add Type[Base]	-0,111303	
Add Type[Ylide]	0,1113035	
Add duration	-0,020446	
Temperature	-0,085241	
Anion[OH]*Add Type[Base]	0,0293049	
Anion[OH]*Add Type[Ylide]	-0,029305	
Anion[tBuO]*Add Type[Base]	-0,029305	
Anion[tBuO]*Add Type[Ylide]	0,0293049	
Anion[OH]*(Add duration-60)	-0,024134	
Anion[tBuO]*(Add duration-60)	0,0241338	
Anion[OH]*(Temperature-70)	-0,028654	
Anion[tBuO]*(Temperature-70)	0,0286538	
Add Type[Base]*(Temperature-70)	-0,096213	
Add Type[Ylide]*(Temperature-70)	0,0962132	
(Add duration-60)*(Temperature-70)	-0,027455	

portion) and at higher temperatures. We therefore sought to develop a reverse addition process at a higher temperature which would allow control of the exotherm through a slow addition of the thermally unstable dimethylsulfoxonium methylide to ethyl crotonate. Alternatively, we also investigated the fractionated addition of base to a hot mixture of ethyl crotonate and insoluble trimethylsulfoxonium iodide in DMSO, resulting in a slow formation of dimethylsulfoxonium methylide over time.

To support the subsequent delivery of a larger scale of material, DMSO was selected as solvent, and the process was further evaluated through a DoE to analyze cation (Na or K), anion (HO^- or *t*BuO^-), addition type (base or preformed ylide), addition rate (40 or 80 min), and temperature (60 or 80 °C).[5] Those variables were studied in 2^{5-1} fractionated factorial design (16 experiments) without center points. We fitted a first-order linear model with five two-factor interactions on the experimental response "yield"with a good fit ($R^2 = 0.987$) (Table 1).

This model emphasized strong main effects of addition type (ylide addition better than base addition) and of temperature (positive effect), and minor effects of cation, anion and addition rate. Strong interactions were also observed especially between addition type and temperature and between addition type and anion (Chart 1).

From this DoE study, we thus defined several possible ways to carry out the reaction. For each of them, the prediction profilers illustrated below (Charts 2−5) summarize the effects of cation, anion, addition-type and -rate, and temperature on expected yield.

1. pre-formation of ylide with *t*$ButO^-$ and addition at 80 °C over 40 min: 56.7 ± 8.5% yield
2. pre-formation of ylide with HO^- and addition at 80 °C over 40 min: 46.4 ± 8.5% yield
3. pre-formation of ylide with HO^- and addition at 60 °C over 40 min : 44.5 ± 7.6% yield (less sensitive to addition duration than process 2)
4. addition of HO^- in four 0.25 equiv fractions at 60 °C over 40 min: 47.3 ± 7.6% yield

The results summarize in above charts clearly indicate that, within the experimental domain defined for the DoE, the best yields were obtained at 80 °C with a fast addition of an ylide pre-formed with *t*$ButO^-$. From that study, we could also explain

Chart 1. **Interaction plot**

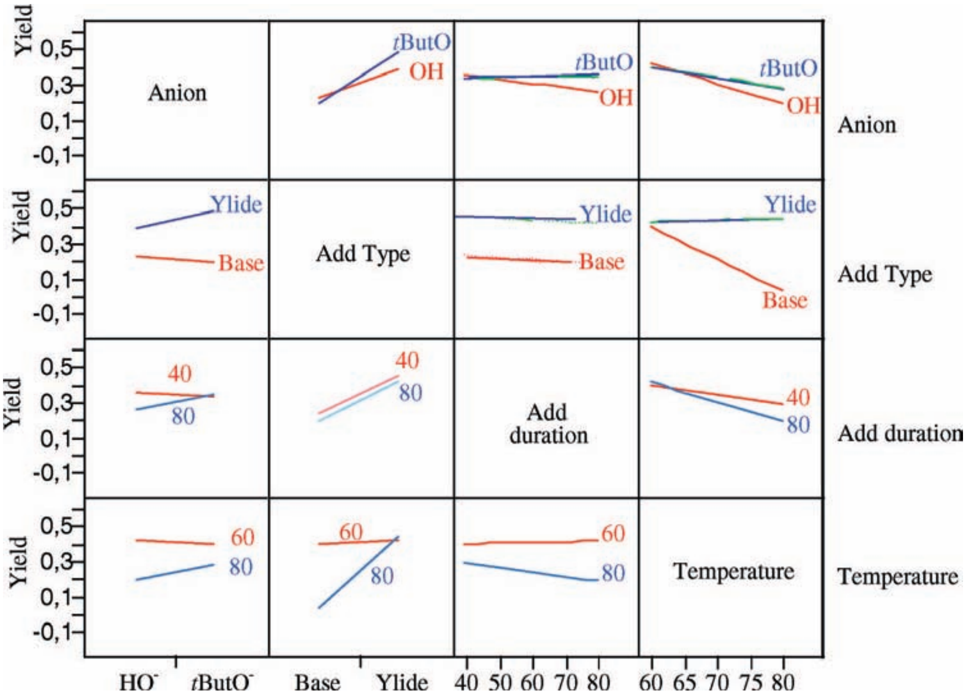
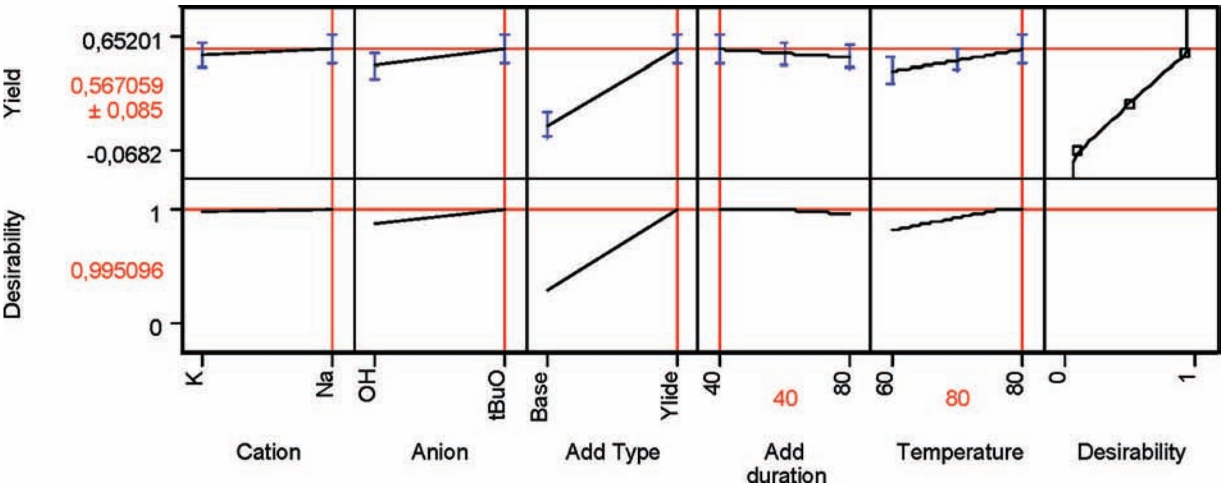


Chart 2. **Prediction profiler for the addition of an ylide pre-formed with *tert*-butoxide at 80 °C**



the difference of performance between the *tert*-butoxide and hydroxide anions in the pre-formed ylide addition process by the presence of water. It is worth to mention that in parallel to the DoE study, we have observed a decrease of the yield from 44% to 35% in a reaction run at 60 °C involving an anhydrous ylide prepared with *t*ButOK to which 1.5 equiv of water was added.

We also hypothesized that the optimum temperature should be above 80 °C and conducted a few more experiments at higher temperature and compared the yields with those obtained in the DoE study. As shown in Table 2, the highest yields were obtained at 95 °C with a fast addition (entry 6) which is in agreement with the conclusions of the DoE. At 120 °C, the yield dropped to 34%, and an incomplete conversion of ethyl crotonate was observed, confirming that decomposition of dimethylsulfoxonium methylide becomes competitive at this temperature.

Although we had previously observed that the use of 1.3 equiv of ylide at 80 °C had no negative impact on the yield (Table 3), we did not evaluate the possible use of such an excess eventually combined with a lower addition rate to achieve a complete conversion of ethyl crotonate at 120 °C. Indeed, these conditions would have resulted in a safety issue due to the potential accumulation of the thermally unstable dimethylsulfoxonium methylide.

Despite significant analytical effort, the structure of most of the impurities formed in the cyclopropanation step is still unknown. Only the major by-product **4**, which is completely removed in the aqueous layers during the workup, has been formally identified by NMR. The formation of **4** (2–5 mol % under the optimal conditions but up to 25 mol % at low temperature) is explained by the pathway illustrated in Figure 1. It is worth mentioning that similar compounds were obtained by Corey.[7] Al-

Chart 3. **Prediction profiler for the addition of an ylide pre-formed with HO⁻ at 80 °C**

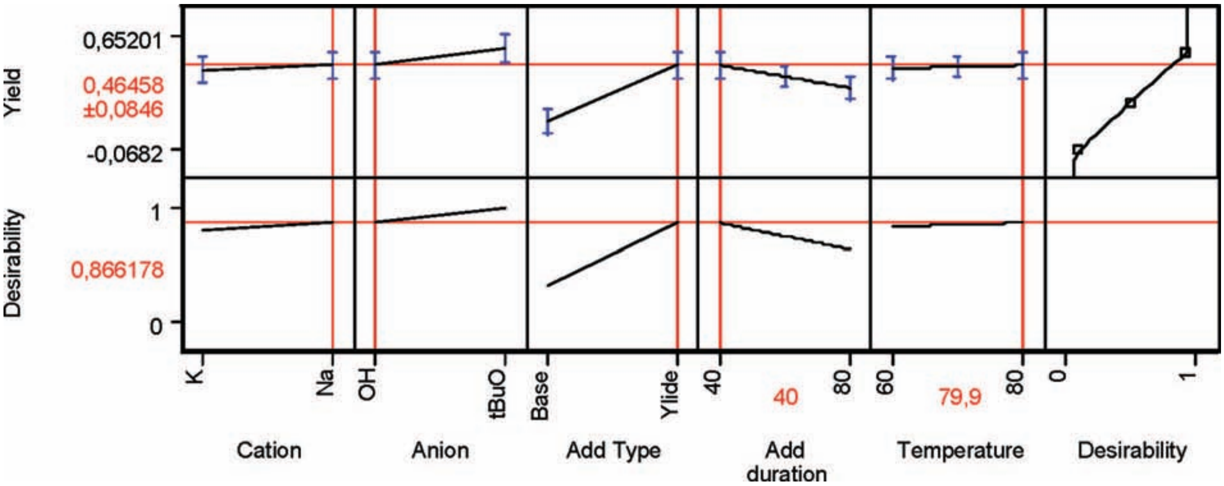


Chart 4. **Prediction profiler for the addition of an ylide pre-formed with HO⁻ at 60 °C**

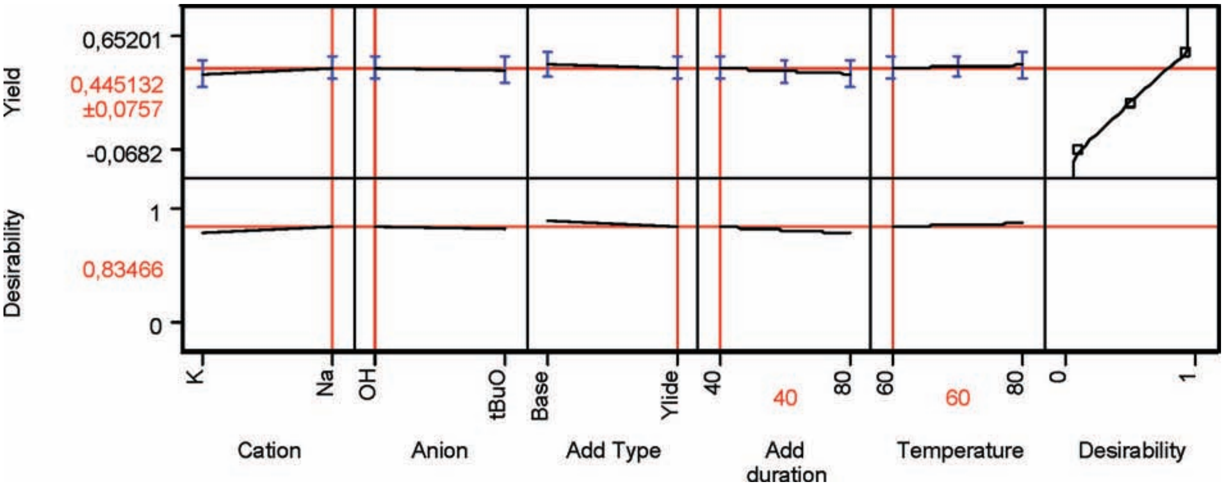
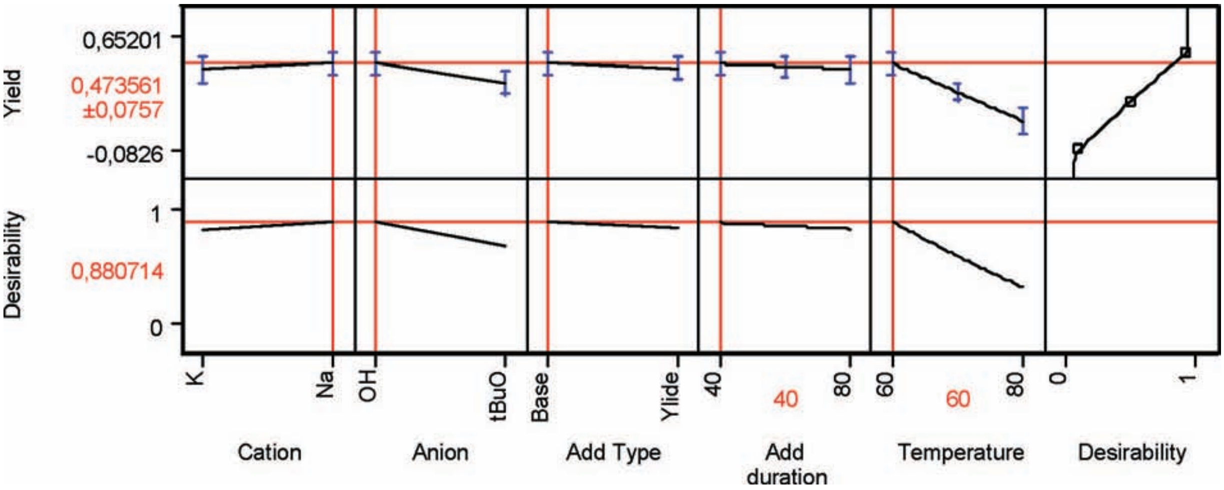


Chart 5. **Prediction profiler for the portion-wise addition of HO⁻ at 60 °C**



though it has been suggested in literature, we did not find any evidence for a 1,2 attack of the unsaturated ester.

From the analytical point of view, in order to avoid the handling of an air- and water-sensitive solution, we monitored the ylide formation using in situ near-infrared technology ($\nu \approx 1060\ \mathrm{cm}^{-1}$). Using the same automated laboratory equipment also allowed us to evaluate the reaction selectivity in situ. The

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(7) (a) Corey, E. J.; Chaykovski, M. *J. Am. Chem. Soc.* **1964**, *86*, 1640–1641. (b) Corey, E. J.; Chaykovski, M. *Tetrahedron Lett.* **1963**, *4*, 169.

Table 2. **Addition of preformed ylide solutions on ethyl crotonate: influence of temperature**

entry	base	temp. (°C)	addition time (min)	yield[a] ^{1}H NMR (%)
1	KOH	60	15	43
2	KOH	60	60	42
3	*t*-BuOK	80	40	47
4	*t*-BuOK	80	15	49
5	*t*-BuOK	95	40	52
6	*t*-BuOK	95	15	56
7	*t*-BuOK	120	15	34

[a] Naphthalene was used as internal standard.

Table 3. **Influence of an excess of ylide**

entry	equiv of ylide	temp. (°C)	addition time (min)	yield[a] ^{1}H NMR (%)
1	0.98	80	15	52
2	0.98	80	80	50
3	1.3	80	120	49

[a] Naphthalene was used as internal standard.

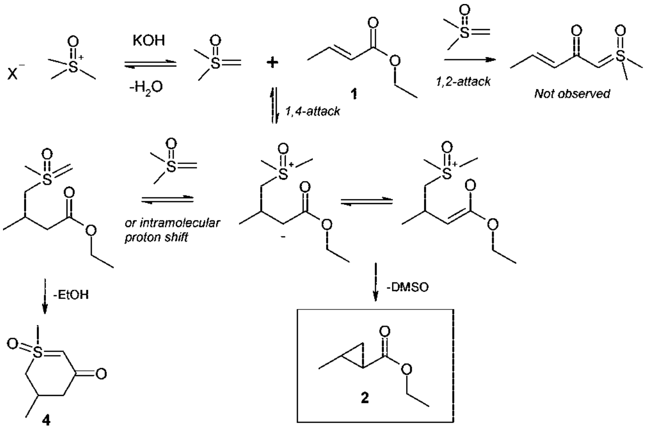

Figure 1. **Reaction mechanism and major side reaction.**

conversion of ethyl crotonate ($\nu \approx 1715$ cm^{-1}) and competitive formation of impurity **4** (several specific bands, e.g., $\nu = 1650$ cm^{-1}) were determined via their relative absorbance over time compared to a standard solution (Figure 2) and double-checked by ^{1}H NMR.

Safety Evaluation

As discussed above, an increase of temperature is beneficial for the cyclopropanation yield and we have identified an optimum around 95 °C. However, in view of a large-scale synthesis, the potential hazardous decomposition of dimethylsulfoxonium methylide was considered, and we decided to perform the process at 80 °C. A thorough safety study was therefore performed at this temperature. The evaluation was first carried out in a RC-1 calorimeter equipped with a React-IR probe under normal operating conditions in order to check and measure the following data: ylide accumulation, adiabatic temperature rise, and heating power generated by the reaction. We then studied the thermal stability via Dynamic DSC[8] and Vent Sizing Package (VSP)[9] in order to have information on a potential decomposition that may occur outside of the normal operating conditions.

A. Normal Operating Conditions. As shown in Figure 3, there was a direct heat flow at the time of the base addition (done in one shot). The heat generated during the addition corresponds to 13 °C of mass temperature rise under adiabatic conditions. The reaction took approximately 1 h to go to completion as indicated by the end of the heat flow and in situ near-infrared technology.

The cyclopropanation reaction generates more than 150 W/kg of reaction mixture (Figure 4). This energy, generated during the initially proposed 40 min addition time, is much too large to be scaled up directly into the pilot plant as the overall heat removal capacity of the reactor is about 30 W/kg of mixture. Consequently, the addition time in the plant was changed to 4 h, and this process was successfully implemented in a 2000-L reactor.

As indicated in Figure 5, there was only a very small accumulation of ylide (ca. 5%) at the end of the addition at 80 °C (the same results were obtained at 20 °C).

The maximum temperature for the synthetic reaction (MTSR) is about 83 °C (Figure 6).[10] It is caused by the accumulated ylide at the end of the addition which quickly decomposes at this temperature (see Table 4). The adiabatic temperature rise for the reaction is about 60 °C.

B. Stress Conditions. Dynamic DSC (at 5 °C/min heating rate) was performed on the different mixtures in order to determine potential decomposition problems (Table 4).

The adiabatic time to maximum rate (TMR$_{\mathrm{ad}}$) is based on a zero-order kinetic model (conservative approach), assuming a thermal power of 10 W/kg and an activation energy of 50 kJ/mol at the decomposition temperature.[11] As shown in Table 4, the ylide solution exhibits two exothermic events. The first one begins near 70 °C and has a TMR$_{\mathrm{ad}}$ < 24 h which is the usual warning threshold, but the thermal consequences are limited ($\Delta T_{\mathrm{ad}} = 40$ °C). In addition, as the ylide solution is air- and water-sensitive, it was decided from the beginning to use it directly in the cyclopropanation reaction. However, a temperature increase has a dramatic effect on the ylide's TMR$_{\mathrm{ad}}$ which drops to 0.3 h at 80 °C. Therefore, the only safe way to perform the cyclopropanation reaction at this temperature is to pump

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(8) For an article dealing with the estimation of the time to maximum rate using dynamic DSC experiments, see Keller, A.; Stark, D.; Fierz, H.; Heinzle, E.; Hungerbühler, K. *J. Loss Prev. Process Ind.* **1997**, *10*, 31. Typically, the sample is heated and cooled several times below its decomposition temperature, and the effect of the number of cycles on the final decomposition temperature is estimated. This method allows to evaluate the potential risks associated with autocatalytic decompositions.

(9) Vent Sizing Package (VSP) is used to determine self-heating rates. It offers better sensitivity than conventional RSST tools. Lab-scale equipment is available from Fauske and Associates, Inc. (www.fauske.com).

(10) Maximum temperature for the synthetic reaction (MTSR) corresponds to the maximum temperature that could be reached by the reaction in case of a deviation to the process (e.g., cooling failure).

(11) Adiabatic time to maximum rate (TMR$_{\mathrm{ad}}$): corresponds to the period of time separating a deviation to the process (e.g., cooling failure) and the exothermic decomposition of the reaction mixture (the greater the TMR, the safer the process).

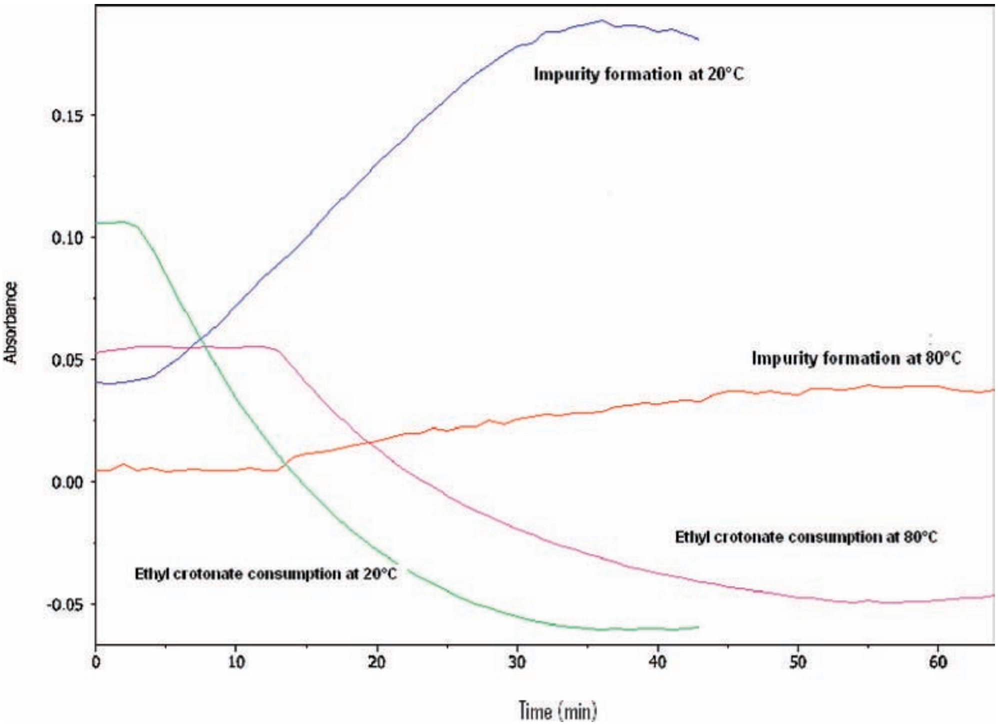

Figure 2. **IR reaction selectivity monitoring.**

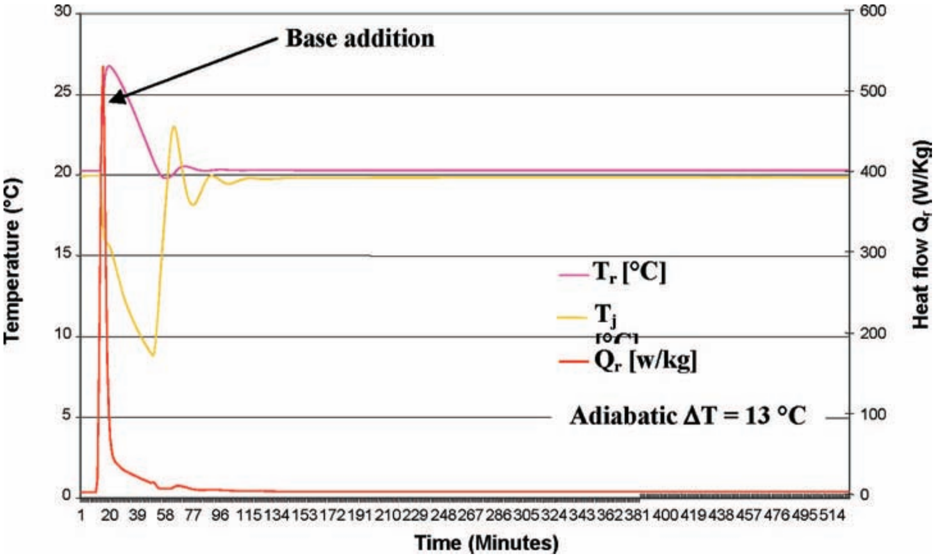

Figure 3. **RC-1 data for ylide formation.**

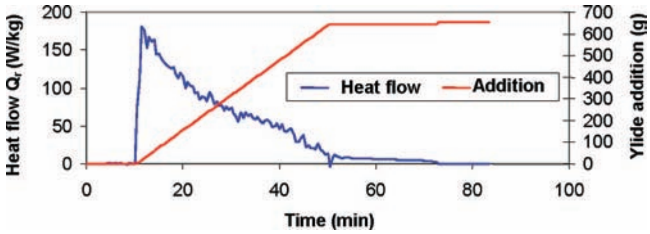

Figure 4. **RC-1 data for cyclopropanation reaction.**

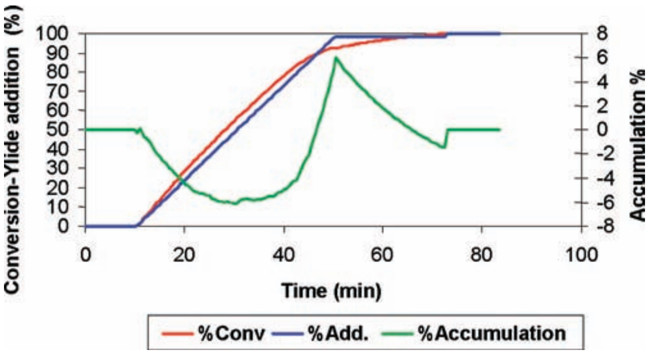

Figure 5. **Cyclopropanation reaction: ylide accumulation.**

slowly the cold ylide solution into the reactor at such a rate that there is no accumulation (dose-controlled reaction).

C. Worst-Case Scenario. An uncontrolled addition of the ylide solution would lead to a reaction temperature of 140 °C (initial reaction T + adiabatic ΔT) which is still under the decomposition temperature of the reaction mixture. At 140 °C, the TMR_{ad} would be about 21 h which is still sufficient to apply

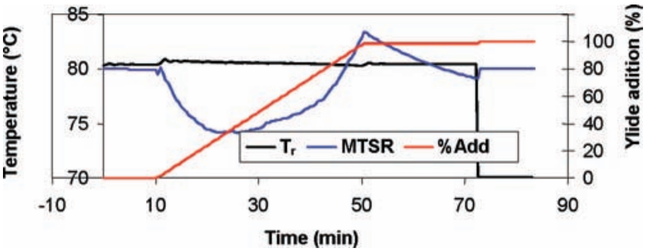

Figure 6. **Cyclopropanation reaction: MTSR.**

Table 4. **Dynamic DSC results**

	first exotherm		second exotherm (decomposition)	
	ΔT_{ad} (°C)	TMR_{ad} (hours)	T_{ad} (°C)	TMR_{ad} (hours at 80 °C)
ylide solution	40	5 (20 °C) 0.3 (80 °C)	160	185
ethyl crotonate solution	–	–	120	540
reaction mixture	–	–	125	230

countermeasures (dilute the reaction mixture, transfer to another reactor, and so forth).

The safety parameters of the ylide formation and cyclopropanation steps can be summarized in Figure 7, where it is mentioned that each step of the process was rated at level 2 (on a scale of 5) which means that they are thermally safe.[12] Indeed, under normal conditions, we should not exceed the MTSR that is well below the 24 h TMR_{ad}.

Before scaling up the process, additional safety data (VSP) were generated for the reaction mixture at 50 and 100% conversion, confirming that these mixtures can be heated up to 150 °C without any sign of hazardous decomposition.

Development of a Telescoped Process

Our initial laboratory studies showed that isolation of ester **2** is challenging because of its relatively low boiling point (bp = 50 °C/40 mbar) and high vapor pressure. For example, up to 10% was lost in the initial large-scale synthesis upon distilling a MTBE solution at 40 °C/150 mbar. In addition, ethyl *trans*-2-methylcyclopropane carboxylate exhibits a particularly penetrating odor which makes its handling particularly inconvenient. The process was thus modified, and the ester **2** was directly hydrolyzed by adding aqueous potassium hydroxide to the crude DMSO solution after the cyclopropanation reaction. Under these conditions, hydrolysis of **2** is completed within 1 h at room temperature. After acidification with HCl, the acid **3** was extracted with various solvents such as MTBE, toluene, or isopropyl acetate. Isopropyl acetate was selected for the large-scale synthesis as it allows another telescoping with the subsequent optical purification step. In addition, we also noticed that most by-products, which were previously removed in the basic aqueous layer upon extraction of **2**, are also eliminated in the acidic aqueous phases upon extraction of **3**. Finally, despite the high proportion of DMSO in the aqueous layers which obviously complicates the extraction, the losses of **3** never exceeded 5%.

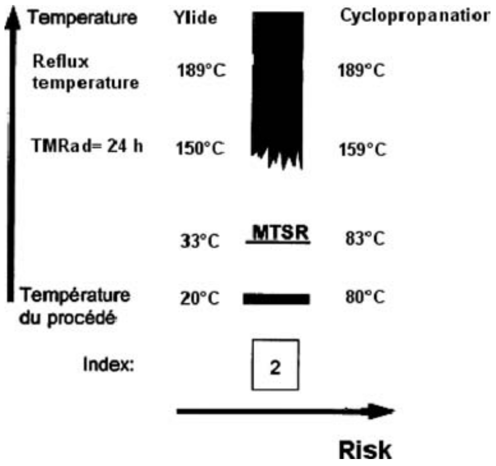

Figure 7. **Safety parameters for ylide formation and cyclopropanation steps.**[12]

Investigations towards a Continuous Process

In order to avoid the potential safety issues associated with the use of dimethylsulfoxonium methylide at high temperatures, we briefly evaluated the use of a continuous flow reactor. The reaction was studied in a plug-flow reactor made of a mixer with either a T-joint or a slit interdigital micromixer SIMM V2-Lasab from Institute für Mikrotechnik Mainz GmbH, coiled stainless steel HPLC tubing and two HPLC pumps from Waters. The reaction was run at 40, 60, 80, and 100 °C in 20 vols of DMSO. The ylide was performed with potassium *tert*-butoxide in 10 vols of DMSO, and the ethyl crotonate was also dissolved in 10 vols of DMSO. The crotonate solution also contained 10 mol% of naphthalene as an internal standard. The two solutions were mixed at different flow rates from 1 to 10 mL/min. After the mixer the reaction was allowed to react for 1 min in the coiled reactor. Prior to mixing, the ethyl crotonate solution was preheated to the desired temperature. The ylide solution on the contrary was kept at room temperature prior to mixing to avoid decomposition.

The result of this detailed study was in our eyes somewhat surprising as we thought at that time that an excess of ylide would facilitate the proton shift in the intermediate to form the impurity **4**. On the contrary, independent of the type of mixer, the flow rate, and the temperature, the results from the

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(12) Following the classification of the Swiss Institute of Safety and Security (www.swissi.ch), Newsletter 2004–1.

(13) *Typical experimental procedure*: Trimethylsulfoxonium iodide (850 g, 3.81 mol) was slurried in DMSO (3 L) under nitrogen. Potassium *tert*-butoxide (410 g, 3.64 mol) was added at once (ca. 10 °C exothermicity occurred at that time), and the mixture became homogeneous. After 1 h of stirring at 20 °C, the ylide was completely formed (React-IR monitoring). A solution of *trans*-ethyl crotonate (400 g, 3.47 mol) in DMSO (1.2 L) was heated to 80 °C. To that solution was slowly added the pre-formed ylide solution over 1 h, maintaining the mass temperature between 75 and 80 °C. The mixture was still homogeneous and became yellow; GC analysis showed <0.1% residual crotonate. The solution was cooled down to 20 °C, and aqueous KOH (255 g, 4.5 mol, in 900 g of water) was added in 15 min, maintaining the mass temperature between 15 and 35 °C. After 2 h, GC analysis showed complete hydrolysis of **2**. Aqueous 1.5 N HCl (3.4 L, 5.1 mol) was added to the mixture, maintaining the temperature between 15 and 30 °C, and the solution was allowed to stand overnight. The aqueous layer was extracted with isopropyl acetate (3 × 2 L). The combined organic layers were washed with 15% aqueous NaCl solution (4 L). The solution was distilled under vacuum (100–120 mbar) with a bath temperature of 45 °C to afford 175 g (1.75 mol, 50%) of **2b** as pale-yellow oil (GC: >98% *trans*). The above procedure was successfully reproduced in the pilot plant (2000 L reactor) to afford 22.8 kg (48%) of **2b** of identical quality.

continuous process were the same as from the semibatch process. Although further development will be necessary before starting a large-scale production, as the yields obtained are comparable with those obtained in the batch process, the use of the continuous flow reactor would be an interesting alternative for safety reasons on large scale. From this investigation we also learned that the use of a continuous flow reactor for development gives a very good indication if the reaction is sensitive towards mixing and if isothermal conditions would be beneficial.

Conclusions

We have developed a scalable process for the synthesis of *trans*-2-methylcyclopropanecarboxylic acid via cyclopropanation of *trans*-ethyl crotonate with dimethylsulfoxonium methylide.[13] The combined utilization of DoE, PAT (in situ near-IR spectroscopy) and calorimetry (RC-1, Dynamic DSC, and VSP) allowed us to define the optimal operating conditions consisting in a slow addition of a cold anhydrous solution of preformed ylide on ethyl crotonate in DMSO at 80–95 °C. The process was safely scaled up in a 2000 L reactor to deliver more than 22 kg of **3** with 48% yield and >98% *trans* selectivity. Finally, similar results were obtained at the laboratory scale via the use of a continuous flow reactor.

Acknowledgment

We thank J. Niemeier (Lilly Chemical Process Research and Development, Indianapolis, IN, U.S.A.) for his support in the safety assessment (VSP studies).

Note Added after ASAP: Luis Casarubios and Mario Barberis were added as authors in the version published on the Internet July 18, 2007.

Supporting Information Available

Additional DoE, analytical and safety data. This material is available free of charge via the Internet at http://pubs.acs.org.

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