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A Short and Efficient Synthesis of (*R*,*R*)-2-Methylcyclopropanecarboxylic Acid

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Abstract:

We report herein a short and efficient synthesis of (*R*,*R*)-2-methylcyclopropanecarboxylic acid via a Horner−Wadsworth−Emmons reaction involving commercially available (*S*)-propylene oxide and triethylphosphonoacetate (TEPA). The TEPA/base/propylene oxide stoichiometry was found critical to achieve high yields. We therefore studied the TEPA anion formation and stability using *in situ* IR spectroscopy. The reaction yield is strongly influenced by the counterion and solvent, whereas high diastereoselectivities are always obtained. Under the best experimental conditions (HexLi/MeTHF/150 °C), crude (*R*,*R*)-2-methylcyclopropanecarboxylic acid is obtained in 85−90% yield with >98% *trans* selectivity.

Introduction

It has been known for a long time that cyclopropane derivatives can be prepared from epoxides via the Horner−Wadsworth−Emmons (HWE) reaction.[1] In recent years, this method has successfully been extended to the preparation of enantiomerically pure *trans*-2-aryl-cyclopropanecarboxylic acid derivatives.[2]

Several methods have been reported to prepare chiral nonracemic 2-methylcyclopropanecarboxylic acid.[3] However, to the best of our knowledge, all these methods have major disadvantages with respect to the development of a large scale process: multistep synthesis,[3a,b,d,e] moderate enantiomeric excess,[3a−c,g] use of expensive chiral auxiliaries,[3d,e,g] and consistently low overall yields.

Herein, we wish to report the development of a short and high-yielding synthesis of (*R*,*R*)-2-methylcyclopropanecarboxylic acid **2b** from commercially available (*S*)-propylene oxide **1** (Figure 1).

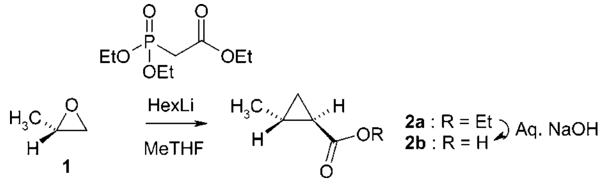
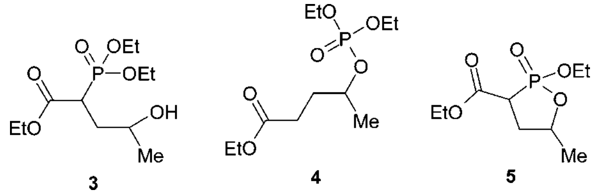


Figure 1.



3 **4** **5**

Figure 2. **Major impurities formed in the reaction of (*S*)-propylene oxide with TEPA anions.**

Results and Discussion

In contrast to the reaction of styrene oxide or related aryl epoxides with anions of triethylphosphonoacetate (TEPA), the utilization of propylene oxide is much more challenging from several points of view: (*i*) alkyl epoxides typically afford only moderate yields of the corresponding cyclopropanes;[4] (*ii*) the low boiling point of propylene oxide may cause technical difficulties unless appropriate pressurized equipment is used;[5] (*iii*) a mixture of *cis*- and *trans*-diastereomers is likely to be obtained due to the potentially weaker steric repulsion between the methyl group and the carbethoxy function.

From the first screening that was perfomed at a 1 mmol scale we restricted the choice of bases to potassium, sodium or lithium alkoxides, alkyl lithiums, and sodium hydride for the subsequent work. Indeed, very low yields were observed with weaker mineral (Cs_2CO_3, K_2CO_3, K_3PO_4, KOH) or organic (LDA, DBU) bases. We also decided to focus on ethereal solvents as low conversions were obtained in hydrocarbons (toluene, xylenes).[6]

During our initial studies, we also noticed the formation of several major byproducts (Figure 2). Impurities **3** and **4** are derived from either a competitive protonation of the alkoxide **6** or carbanion **8** intermediates illustrated in the mechanism proposed below (Figure 3).[2b,3f] Impurity **5** results

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(5) Under our optimal conditions (HexLi/MeTHF/150 °C), a pressure of 10 bar is obtained with a reactor filled at one-third of its volume. The use of *t*-BuONa at 110 °C allows lowering the pressure at 4 to 5 bar.

(6) Low conversions in hydrocarbons were attributed to the formation of very thick slurries resulting in bad mixing.

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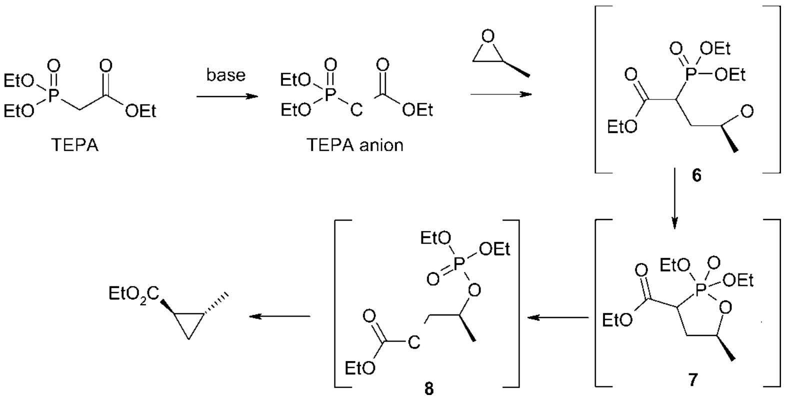

Figure 3. **Proposed mechanism for the reaction of (*S*)-propylene oxide with TEPA anions.**

Table 1. **Effects of Key Reaction Parameters on Yield (2a) and Diastereomeric Ratio (2b)**[a]

entry	base	solvent	*T* (°C)	**2a** yield (%)	**2b** *trans:cis* (yield %)
1	NaO^{t}Bu	MeTHF	110	63	97.1:2.9 (60)
2	NaO^{t}Bu	MTBE	110	53	96.8:3.2
3	NaO^{t}Bu	THF	110	36	97.4:2.6
4	NaO^{t}Bu	dioxane	110	53	98.0:2.0
5	NaO^{t}Bu	diglyme	110	47	97.4−2.6
6	NaO^{t}Bu	MeTHF	130	51	97.2:2.8
7	NaO^{t}Bu	MeTHF	150	47	97.1:2.9
8	NaH	MeTHF	110	48	97.5:2.5 (40)
9	KO^{t}Bu	MeTHF	80	30	95.0:5.0
10	LiO^{t}Bu	MeTHF	150	64	98.4:1.6
11	BuLi	MeTHF	150	84	98.6:1.4 (80)
12	BuLi	MeTHF	150	87	98.7:1.3 (82)
13	HexLi	MeTHF	150	95	98.2:1.8 (90)
14	HexLi	MeTHF	170	92	98.0:2.0 (85)
15	HexLi	dioxane	150	77	98.9:1.1
16	HexLi	diglyme	150	78	98.0:2.0

[a] Reaction conditions: 1.0 equiv of TEPA, 1.0 equiv of base, 1.0 equiv of propylene oxide in 2 mL of solvent/mmol of propyelene oxide in a 160 mL Parr stainless steel reactor with overhead stirring at the indicated temp for 18 h. A heating rate of 10 °C/min was used except for entry 12 (3 °C/min).

from the displacement of an ethoxy group from the phosphorous atom of **7**.

In addition, in our hands, the use of ethereal solvents appeared critical to achieve high yields although the use of xylenes has been reported in the literature.[2a]

Larger scale experiments were then performed in 160-mL stainless steel Parr reactors equipped with overhead stirrers. The yields of ester **2a** were determined by ^{1}H NMR using naphthalene as an internal standard.[7] A typical ^{1}H NMR spectrum of a crude sample is available as Supporting Information. The diastereomeric and enantiomeric excesses were determined by chiral GC on the isolated acid **2b**.

As shown in Table 1, with the exception of the potassium anion of TEPA (entry 9), high diastereoselectivities were obtained in all experiments. Counterion (Li > Na ≫ K) and, to a lesser extent, solvent (MeTHF > diglyme ≈ dioxane ≈ MTBE > THF) have a significant effect on the yield. In-process controls at the beginning of some reactions (1 and 2 h) have shown that propylene oxide is quickly converted while only small amounts of **2a** are detected together with much larger peaks of **3**, **4**, and **5**. This is in agreement with a rate-limiting cyclopropane ring closure and the probable formation of a stable chelate intermediate (Figure 4). This latter could explain the high diastereoselectivities obtained despite relatively moderate steric effects.

In this regard, we investigated the possibility of completing the TEPA anion addition at 75 °C (Na) or 100 °C (Li) prior to heating the reaction mixture to 110 °C (Na) or 150 °C (Li). However, this modification did not result in any improvement of the yield.

Although only moderate yields were obtained with alkoxides, a dramatic improvement was observed with alkyl lithiums. An up to 95% yield was indeed obtained with hexyl lithium at 150 °C. We therefore assume that the presence of *tert*-butanol in the experiments involving *tert*-butoxides leads to the formation of increased levels of impurities **3** and **4** by protonation of intermediates **6** and **8** as observed initially with protic bases. It is also worth mentioning that thick slurries (consisting likely of sodium- or lithium-diethylphosphate) were observed at the end of all the reactions. However, no negative impact on the outcome of the reactions was evidenced as indicated by the high conversions obtained. Noteworthy, lower yields were obtained with NaO^{t}Bu upon increasing the temperature (entries 1, 6−7). In the experiments performed at 130 and 150 °C, we noticed the formation of several unidentified byproducts which could explain the drop of yield.[8] Fortunately, most of these unknown compounds were not observed in the experiments involving lithium-TEPA, although the reactions were run at 150 °C to achieve a complete conversion in 16−18 h. Obviously, this elevation in temperature also had an impact on the reaction pressure. Pressures up to 10 bar were measured in MeTHF using a reactor filled at one-third of its maximum capacity. In this regard, the use of dioxane or diglyme as higher boiling point solvents would have been beneficial to lower the reaction pressure, but we decided to move forward with MeTHF as it gives the highest yields and allows a much easier recovery of **2b** after hydrolysis

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(7) For the first experiments, the yields of **2a** were cross-checked by GC and ^{1}H NMR on isolated material. The differences typically observed (~5%) were attributed to the volatility of **2a**.

(8) GC- and LC-MS analyses on isolated **2a** indicated the possible formation of di- and oligomers from byproducts **3**, **4**, and **5**. Traces of *tert*-butyl ester were also detected.

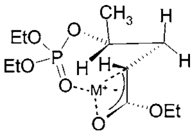

Figure 4. **Chelation effect proposed to explain the high diastereoselectivities.**

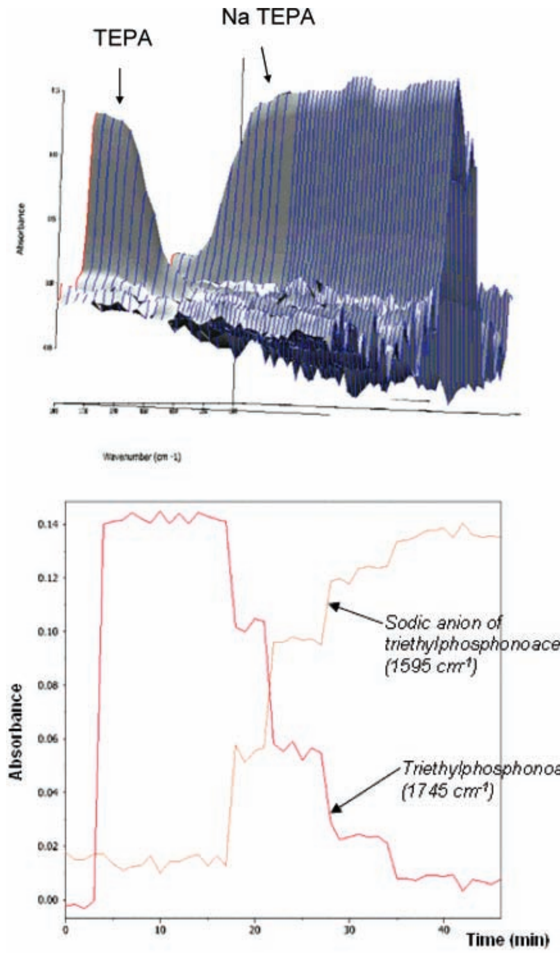

Figure 5. **In situ IR monitoring of TEPA anion formation.**

(*vide infra*). On the other hand, inexpensive and nonhazardous sodium *tert*-butoxide is also worth considering as a potential substitute for alkyllithium.

In the preliminary studies, we had observed that the TEPA/base/propylene oxide stoichiometry is critical to achieve high yields. Indeed, although a large excess of TEPA anion can be used without a significant drop of yield, an excess of strong base causes a fast polymerization of propylene oxide. On the other hand, with a substoichiometric amount of base, the excess TEPA protonates the opened intermediate preventing cyclopropane ring formation and leading to an incomplete conversion of propylene oxide. As such a narrow stoichiometry adjustment is sometimes challenging with strong bases. We used *in situ* IR spectroscopy to monitor the anion formation (Figure 5). This methodology allowed a better understanding of the fast kinetics of the TEPA anion formation ("dose-controlled") and an easy assessment of the reaction completion and TEPA anion stability.

Although isolation of ester **2a** is easily achievable by distillation,[9] we found it much more convenient to directly hydrolyze ester **2a** to acid **2b** using aqueous NaOH at reflux for 4 h. In this regard, the use of MeTHF offers the additional advantage of allowing the elimination of several byproducts when separating the organic layer from the water-soluble sodium salt of **2b**.[10] After acidification with concentrated HCl, the free acid **2b** was extracted with isopropylacetate. Alternatively, toluene or MTBE can be used.

Under our current best experimental conditions, isolated yields ranging from 85 to 90% were obtained (up to 5% **2b** is lost in the aqueous layers). The quality of **2b** at this stage was sufficient for further processing in the subsequent step of the synthesis of a compound in clinical development.[11] If needed, further purification of **2b** can also be achieved by known methods such as distillation[4b] or crystallization as quinine salt.[12] It is worth mentioning that quinine has previously been used for the optical resolution of racemic *trans*-2-methylcyclopropanecarboxylic acid. This latter method was initially compared with the present "chiral pool" synthesis. However it was not judged competitive as it affords optically pure *trans*-2-methylcyclopropanecarboxylic acid in only 25% yield after four crystallizations in acetone.[12] Alternatively, we have found that **2b** can be crystallized as its dicyclohexylamine salt in isopropylacetate with 70% overall yield from (*S*)-propylene oxide (>99.5% ee, >98% de).

In conclusion, we have developed a short and efficient synthesis of (*R*,*R*)-2-methylcyclopropanecarboxylic acid from commercially available (*S*)-propylene oxide and triethylphosphonoacetate. Although unoptimized, isolated yields of **2b** range from 85 to 90% under the current best experimental conditions. Depending on the level of purity needed in subsequent steps, **2b** can either be used crude or

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[9] Bp = 50 °C/40 mbar.

[10] MeTHF solubility in water at 20 °C = 14 g/100 g; water solubility in MeTHF at 20 °C = 4 g/100 g. For a study of MeTHF as efficient process solvent, see: Aycock, D. F. *Org. Process Res. Dev.* **2007**, *11*, 156.

[11] *Typical experimental procedure*: Under a nitrogen atmosphere, *n*-hexyllithium (2.3 M in hexanes, 8 mL, 0.0184 mol) is added dropwise over 20 min to triethylphosphonoacetate (4.5 g, 0.0197 mol) in 40 mL of anhydrous 2-methyltetrahydrofuran keeping the temp between 19 and 25 °C. After 30 min, propylene oxide (1.17 g, 0.0202 mol) is added, and the mixture is transferred into a 160 mL Stainless Steel Parr reactor equipped with a 14 bar rupture disk (we never charged the reactor above one third of its volume for the present procedure). The mixture is heated to 150 °C within 15 min and stirred at this temp for 16 hours at which time ^{1}H NMR analysis of the crude mixture with naphthalene as internal standard indicates >95% molar yield (see ^{1}H NMR spectra and GC chromatograms as Supporting Information). Water (50 mL) and 30% NaOH (25 mL) are added, and the biphasic mixture is stirred at reflux for 5 hours. The layers are separated, and the organic phase is discarded. Aqueous 37% HCl (25 mL) is added to the aqueous layer, and the mixture is extracted with isopropylacetate (2 × 50 mL). The organic layer is washed with 10% NaCl (3 × 25 mL) and evaporated under a vacuum to yield 1.70 g of (*R*,*R*)-2-methylcyclopropanecarboxylic acid (**2b**) as a colorless oil (ca. 95% chemical purity by ^{1}H NMR; >99.5% ee and >97.0% de by chiral GC; see 1H NMR spectra and GC chromatograms as Supporting Information). *Further purification of* ***2b*** *can be achieved by crystallization as dicyclohexylamine salt*: To the above solution of crude **2b** in isopropylacetate is added dicyclohexylamine (3g, 0.0165 mol). A heavy precipitation is observed after 5 min, and the suspension is stirred overnight at 20 °C. The crystals are filtered, washed with isopropylacetate (4 mL), and dried at 40 °C under a vacuum (3.4 g, 66% overall yield, >99.5% ee and >98% de by chiral GC; see ^{1}H NMR spectra and GC chromatograms as Supporting Information).

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purified by various methods. The process has recently been scaled-up to prepare 6.25 kg of **2b**.[13]

Acknowledgment

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Supporting Information Available

Analytical data for the synthesis of **2b**, safety studies, and React-IR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Safety studies (adiabatic T° rise calculation and VSP) have been performed before moving forward with the scaleup (6.25 kg). Details are included as Supporting Information