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Article

A Robust and Scalable Process for the Synthesis of Substantially Pure Clarithromycin 9-(*E*)-Oxime with an Established Control of the (*Z*)-Isomer Impurity

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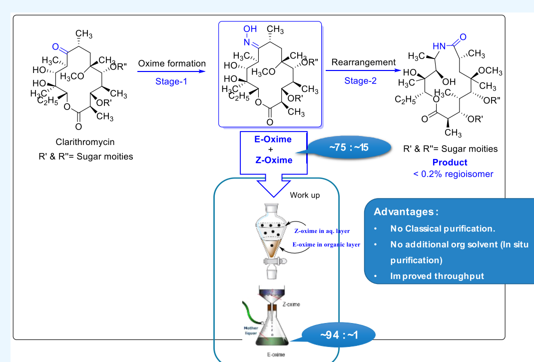
ABSTRACT: Controlling the isomeric impurity in a key raw material is always critical to achieve the corresponding pure isomer-free targeted active pharmaceutical ingredient (API) in downstream processing. Clarithromycin 9-(*E*)-oxime is the key raw material for the synthesis of the 9a-lactam macrolide, which is an interesting scaffold for the synthesis of several bioactive macrolides. Here demonstrated is a scalable process for the preparation of substantially pure clarithromycin 9-(*E*)-oxime, with less than 1.2% of the (*Z*)-isomer. The process does not involve a separate time-consuming purification by a crystallization operation to purge the undesired (*Z*)-oxime isomer. Further, the pure clarithromycin 9-(*E*)-oxime obtained was subjected to the Beckmann rearrangement, thereby converting it into the pure 9a-lactam scaffold. Additionally, a few other impurities were identified and controlled at each stage. The fine-tuned process was successfully up scaled to a multikilogram scale, enabling the large-scale manufacturing of potential APIs derived from this scaffold.



INTRODUCTION

Most of the macrolide compounds or their derivatives such as clarithromycin, erythromycin, and azithromycin, possess antibacterial activity.[1] Initially, it was limited to this therapeutic category only. However, recently other therapeutic areas have been discovered and developed,[2] providing a new window to test these compounds or their derivatives for other therapeutic areas by exploiting their immunomodulatory properties. It has been shown that the reduction of the antibacterial activity of certain macrolides through chemical modification does not necessarily diminish their immunomodulatory potential.[3] As far as the synthesis of such a macrolide is concerned, most of the synthesis routes for the derivatization start with formation of (*E*)- or (*Z*)-oximes.[4] Oxime derivatives of macrolides such as clarithromycin are well-known in the literature.[5] However, controlling the undesired isomer without any additional purification operation along with other related impurities in macrolides has not been much explored for large-scale manufacturing. Though macrolide ketones (erythromycin, clarithromycin, etc.) are readily available commercially, the commercialization of the (*E*)- or (*Z*)-oxime derivatives has not been given much needed attention. A selective scalable process for these oximes (*E* or *Z*) would significantly ease the further development of compounds derived from them, since the orientation of an oxime defines the regioisomer content in the lactam obtained after a Beckmann rearrangement.[4] The obtained macrolide from the Beckmann rearrangement is an interesting moiety used for the synthesis of potential bioactive compounds.

RESULTS AND DISCUSSION

Process Optimization. The most common route[6] for the synthesis of any oxime involves the treatment of a ketone with hydroxylamine in a polar solvent.

Hence, during initial screening, a classical approach of oximation was attempted in methanol as a reaction solvent with 20 equiv of hydroxylamine hydrochloride without using any base, as indicated in Figure 2. Unfortunately, the results were not quite encouraging. LCMS analysis indicated an unexpected mass number [M + H = 606]. The mass number corresponded to the decladinosylated 9-oxime **5** or **6**, as pictured in Figure 3.

This result led us to conclude that implementation of a classical approach of oximation poses a threat for our compound. The presence of acid-sensitive labile sugar moieties as well as the likelihood of the formation of the corresponding

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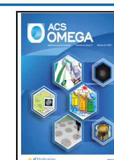

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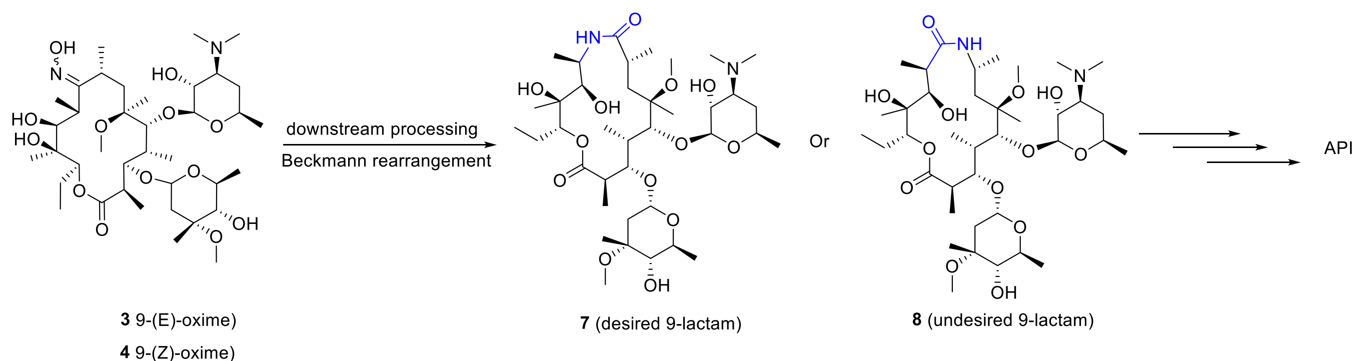

Figure 1. Pathway of potential bioactive substances from clarithromycin 9-oxime through 9-lactam.

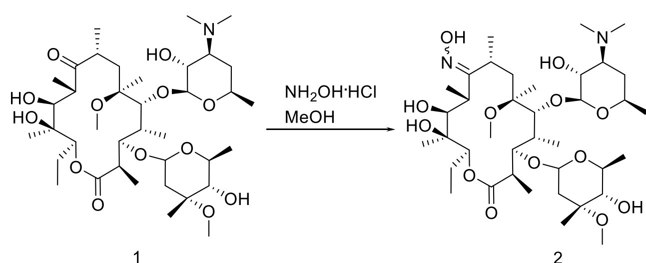

Figure 2. A general approach for oxime formation.

isomeric impurities made the development of the optimum reaction conditions more challenging.

Based on above results, pH appears to be one of the critical process parameters, hence screening at various pH levels was performed. Table 1 indicates the reaction profiles at various pH levels. Entry 1 (pH ∼ 3.1) was an experiment in the absence of a base that resulted in the formation of ∼50% of decladinosylated 9-(*E*)-oxime. It is evident that the labile group in the macrolide does not survive under acidic conditions. The result drove us to narrow down the pH screening to a range of 6−9, i.e., toward more neutral and basic conditions.

As can be seen from Table 1, entry 3 shows good control over the decladinosylated impurity (∼2%) when the reaction was conducted at a pH of 8.4.

However, the daunting challenge that still laid ahead of us was to consume a maximum amount of the clarithromycin **1** during the conversion. In case of entry 3, the amount of unreacted clarithromycin **1** was observed to be ∼5%, as compared to ∼1.2% in entry 4. The presence of unreacted clarithromycin **1** in entry 3 may be attributed to a possible pH-dependent equilibrium between **1** and **2.** On the other hand, the formation of the desired product (∼74%) and decladinosylated impurity **5** were comparatively higher (∼4%) in the case of entry 4. The overall reaction profile led us to conclude that the formation of the decladinosylated impurity is inevitable, which further increases in proportion with the consumption of clarithromycin **1**. Hence, from the above results and observations, the optimal pH parameter was proposed to be in the range of 7−8.

In view of gathering more understanding on the role of base in the conversion, a few commonly used bases were evaluated, such as NaOAc, DIPEA, DABCO, DBU, $NaHCO_3$, K_2CO_3, and *tert*-BuOK. As shown in the Table 2, different bases were explored in different solvents. Methanol was selected as a preferred solvent due to literature precedent.[4] Among these, promising results were obtained with sodium acetate trihydrate in the presence of 0.5 equiv of sodium bicarbonate in methanol. Surprisingly, in the cases of entry 3−9, >50% clarithromycin **1** remained unconsumed without or with the formation of the minor desired product. These results also lead use to conclude that a comparatively weaker base is necessary to facilitate the conversion and a pH adjustment of ∼7−8 is a critical factor for controlling the impurity and pushing the reaction toward completion. These observations were also supported by the data of Table 1. Here the role of sodium bicarbonate was to adjust and maintain the pH.

Further, to optimize the equivalents of hydroxylamine and base, sodium acetate trihydrate was kept as a fixed base. To facilitate the good conversion of clarithromycin **1** to the corresponding oxime **2**, equivalent of reagents and bases were screened from 2.5 to 25 mol equiv in a 1:1 ratio.

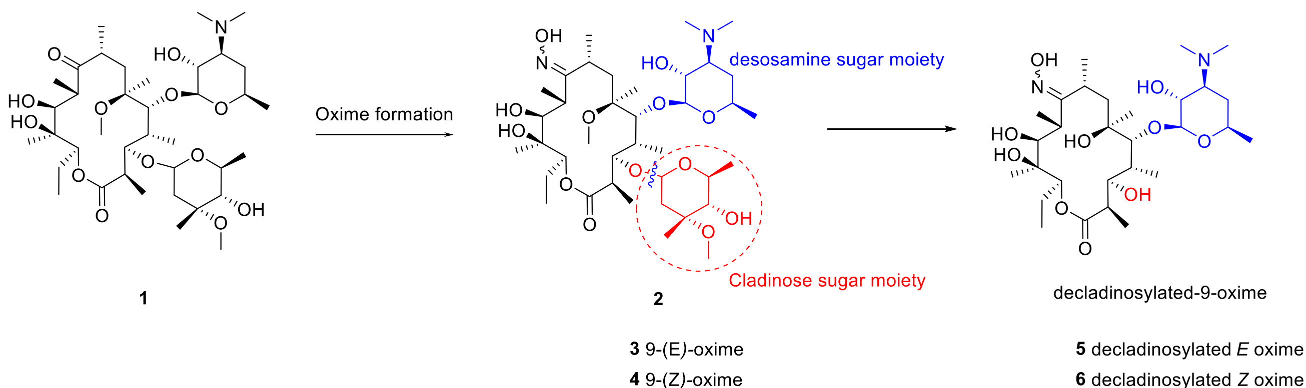

Figure 3. Pathway indicating the formation of a decladinosylated oxime.

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ACS Omega 2023, 8, 10411−10418

Table 1. Effect of pH on the Reaction Profile

entry	$NH_2OH·HCl$ (equiv)	$NaOAc·3H_2O$ (equiv)	$NaHCO_3$ (equiv)	pH	reaction monitoring HPLC analysis (% area)				
					1	**3**	**4**	**5**	**6**
1	20			3.1	0.12			50.78	8.3
2	20	20		6.1	1.72	61.09	13.31	16.50	1.2
3	20	20	3	8.4	5.12	73.41	16.23	2.15	0.31
4	20	20	0.5	7.7	1.19	74.44	16.10	4.0	0.42

Table 2. Screening of Bases in Various Solvents[a]

entry	base (equiv)	solvents (M)	reaction monitoring by HPLC (% area)			
			1	**3**	**4**	**5**
1	NaOAc (20)	MeOH (5)	1−2	60−75	14−17	4−17
2	$NaOAc·3H_2O$ (20) $NaHCO_3$ (0.5)	MeOH (5)	1−2	71−75	14−16	2−5
3	DIPEA (15)	MeOH (3)	70	ND	ND	ND
4	DABCO (15)	MeOH (3)	87	ND	ND	ND
5	DBU (10)	THF (10)	72	ND	ND	ND
6	K_2CO_3 (10)	THF (10)	53	ND	ND	ND
7	^tBuOK (10)	THF (10)	65	1.3	ND	4.1
8	$NaHCO_3$ (20)	MeOH (5)	55	4	ND	ND
9	K_2CO_3 (20)	MeOH (5)	60	ND	ND	ND

[a]ND = not detected.

Table 3. Screening of Equivalents of $NaOAc·3H_2O$ and $NaHCO_3$ in Methanol (5 M) as a Solvent[a]

entry	$NH_2OH·HCl$ (equiv)	$NaOAc·3H_2O$ (equiv)	$NaHCO_3$ (equiv)	reaction monitoring by HPLC (% area)			
				1	**3**	**4**	**5**
1	2.5	2.5		30	34	11	0.2
2	5	5		17	58	16	1−2
3	10	10		5.6	68	16	2.3
4	10	8		6.4	71	17	1.9
5	10 + 3	10 + 3		3.3	74	15	3.0
6	15	15		5.8	71	17	2.3
7	20	20		0.9	73	16	6.1
8	20	23		1.6	70	15	4.7
9	25	25		1.2	74	16	5.8
10[b]	20	20	0.5	1.2	74	16	4.0
11[b]	20	20	3	5.1	73	16	2.2

[a]All experiments were performed on a 25−50 g scale. [b]Scouting experiments were performed after 1 kg batch failure using conditions in entry 7.

From entry 1 to entry 7 in Table 3, the equivalents of sodium acetate trihydrate and hydroxylamine hydrochloride were increased gradually. Increasing the equivalents improved the conversion, as can be seen from the results of entries 1−3. However, no further increase in the conversion were observed even when reagent quantities were increased from 10 to 15 equiv (entries 3 and 6, respectively). Surprisingly, when the part addition was performed (entry 5) with 10 equiv at the beginning of the reaction followed by additional 3 equiv after 20 h of reaction monitoring, the starting material consumption (∼3%) was comparatively better than initial entries. However, it badly impacted the cycle time (48 h for conversion). Hence, it was decided to increase the equivalent (>15) of the reagents further. As expected, increasing the equivalents (∼20) of both the reagents (entry 7) provided almost complete (∼ 0.90%) consumption of the starting material **1** within 24 h. Unfortunately, the level of decladinosylated impurity **5** was comparatively higher (∼6%). Further increasing the equivalents of reagents (25 equiv, entry 9) did not help much to improve the conversion profile. Hence, entry 7 was considered as an optimum parameter.

Nevertheless, the above developed process parameters were tested first on a 1 kg scale. Disappointingly, unacceptable levels (∼20%) of **5** were observed during the process monitoring. Upon investigation, it was revealed that the pH of the reaction mixture was ∼4. Despite the large excess of base (sodium acetate trihydrate), the formation of **5** was surprising. Hence, further fine-tuning of the process was undertaken. The conversion was explored by adding 0.5−3 equiv of sodium bicarbonate in the reaction mixture (entry 10 and 11) to maintain the pH toward the neutral or basic side. From the results of entries 10 and 11, it was clear that reaction profile with 0.5 equiv (entry 10) of sodium bicarbonate was comparatively better than that with 3 equiv (entry 11). When these conditions (entry 10) were implemented on a 1 kg scale, we were delighted to achieve the desired conversions with control over the decladinosylation during the reaction.

With these promising results, the finalized optimum reaction conditions were evolved as 20 equiv each of hydroxyl amine

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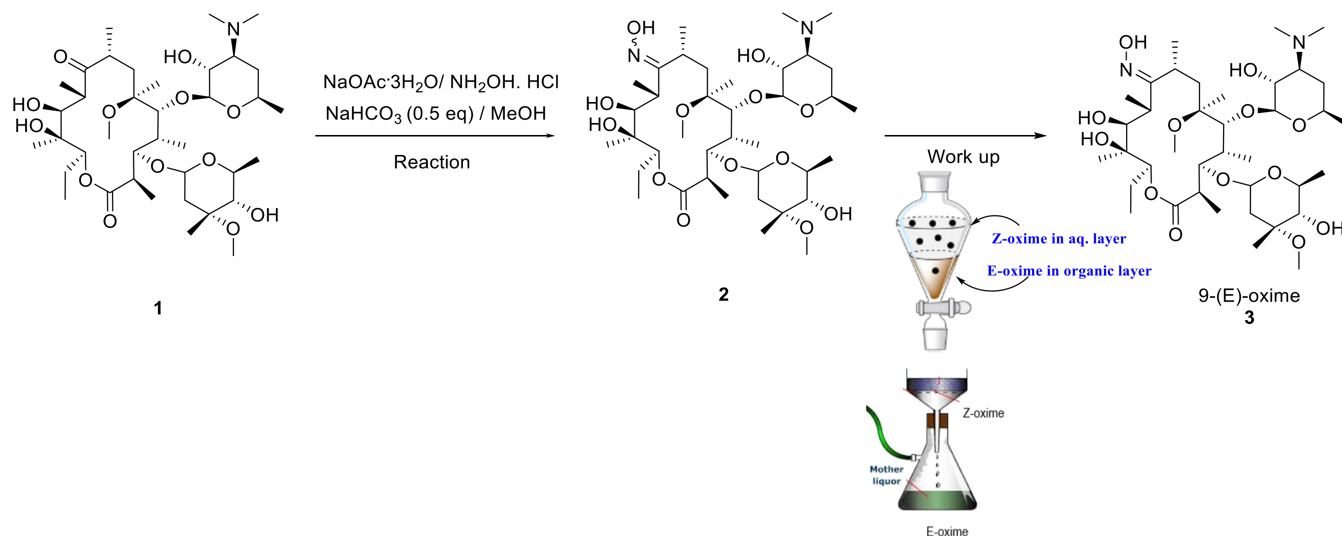
Scheme 1. Conversion of Clarithromycin to Substantially pure 9-(*E*)-Oxime during Work Up Processing



hydrochloride and sodium acetate trihydrate in the presence of 0.5 equiv of sodium bicarbonate in methanol (5 M).

Having identified the bases, equivalents, and solvent for efficient conversion, the next challenge was to control the levels of undesired (*Z*)-isomer **4** in the isolated solid product.

It is known in the literature that the (*E*)- and (*Z*)-isomers of an oxime can be separated by crystallization in a halogenated solvent[7a] or in combination with a cosolvent such as chloroform/heptane.[7b] This observation led us to plan the screening of various solvents for the work up. We replaced chloroform with dichloromethane (DCM) for comparative ease of handling.

During reaction monitoring, both the (*E*)-isomer **3** (~75%) and the (*Z*)-isomer **4** (~15%) of oxime were formed, with kinetic selectivity toward the (*E*)-isomer. Several solvents such as DCM, toluene, ethyl acetate, MTBE, MeOAc, i-PrOAc, *n*-BuOAc, and i-BuOAc were explored for the selective removal of (*Z*)-oxime **4** by extraction. It was found that the aqueous layer became turbid during work up when DCM was used as a solvent for extraction, and it subsequently became clear upon filtration, as depicted in Scheme 1 graphic. The analysis of the organic layer (DCM) from the mother liquor was very encouraging because the undesired isomer ((*Z*)-oxime) was observed only to the extent of 1−1.2% with the (*E*)-oxime (~90−95%).

This observation was unique to the usage of DCM and is supported by solubility data of (*E*)-oxime and (*Z*)-oxime in various solvents, as mentioned in below Table 4

DCM/water extraction provided an acceptable purging of the undesired (*Z*)-isomer **4**. The basis behind the separation could be the difference in the solubility of (*E*)-isomer **3** versus that of (*Z*)-isomer **4**. Due to the poor solubility of **4** in DCM (entry 1), it remained in the aqueous layer during work up (pictorial representation as in reaction Scheme 1). That could be the reason why the aqueous layer was observed to be turbid. Though the solubility result for (*Z*)-oxime in ethyl acetate was comparative with that of DCM, the solubility of (*E*)-oxime was comparatively higher in DCM than ethyl acetate. Therefore, DCM was finalized as a solvent of choice.

Further, to remove other impurities such as clarithromycin **1** and decladinosylated oximes **5** and **6**, a purification technique was developed in IPA. Overall, with these operations,

Table 4. Solubility of Compounds (mg/mL) at 20−30 °C[a]

entry	solvent	oxime 3	oxime 4
1	dichloromethane	~125	<5
2	toluene	~20	~10
3	MTBE	~40	~12
4	EtOAc	~60	~10
5	MeOAc	~25	~14
6	*i*-PrOAc	~16	~15
7	*n*-BuOAc	~14	~11
8	*i*-BuOAc	~12	~11

[a]Solubility was determined based on the amount of solvent required for complete dissolution (visually) on a 0.5 g scale for each solvent.

substantially pure (*E*)-oxime **3** (purity> 95%) was obtained with very low levels (<1.2%) of undesired isomer **4**, and the amount of other related impurities were restricted to <0.2%.

Three major impurities **4**−**6** were confirmed by comparing them with the reference compounds prepared (as shown in Figure 4) and characterized by ^{1}H NMR and LCMS.

Beckmann Rearrangement. Further, the (*E*)-oxime **3** prepared with the optimized conditions was subjected to *p*-TsCl-catalyzed Beckmann rearrangement, as depicted in Figure 1. Typically, (*E*)-oxime **3** was treated with *p*-TsCl at −20 to 0 °C in acetone and an aqueous sodium bicarbonate solution. After the completion of the reaction, the pH was adjusted between 10 and 13 and the solvent was removed. Further work up provided crude 9a-lactam (**7**). During conversion, the amount of the regioisomer of lactam was observed to be in the range of 0.9 to 1.2%, which then was purified by IPA/*n*-heptane precipitation technique to obtain >98.4% pure desired lactam with <0.10% of undesired isomer **8**, along with <0.20% of all other individual impurities (specifically **9**−**12**, as shown in Figure 5). Downstream conversion has proved that the obtained (*E*)-oxime with the optimized process was of acceptable quality.

As a comparative study, one of the rearrangement experiments was performed with a relatively higher (~2%) content of (*Z*)-oxime in (*E*)-oxime. During the conversion to 9a-lactam, the amount of the regioisomer of lactam **8** was ~1.63%, which subsequently reduced to 1.2% in the crude solid and further to 0.24% after purification. Hence, from this

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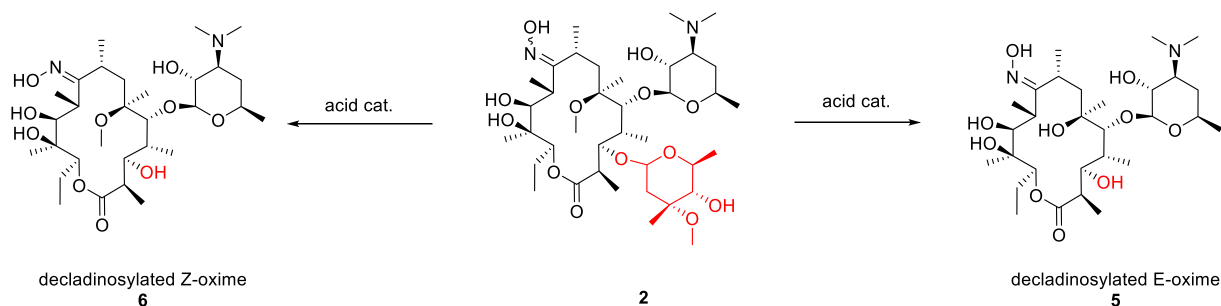

Figure 4. Preparation of decladinosylated 9-(*E*)-oxime and 9-(*Z*)-oxime.

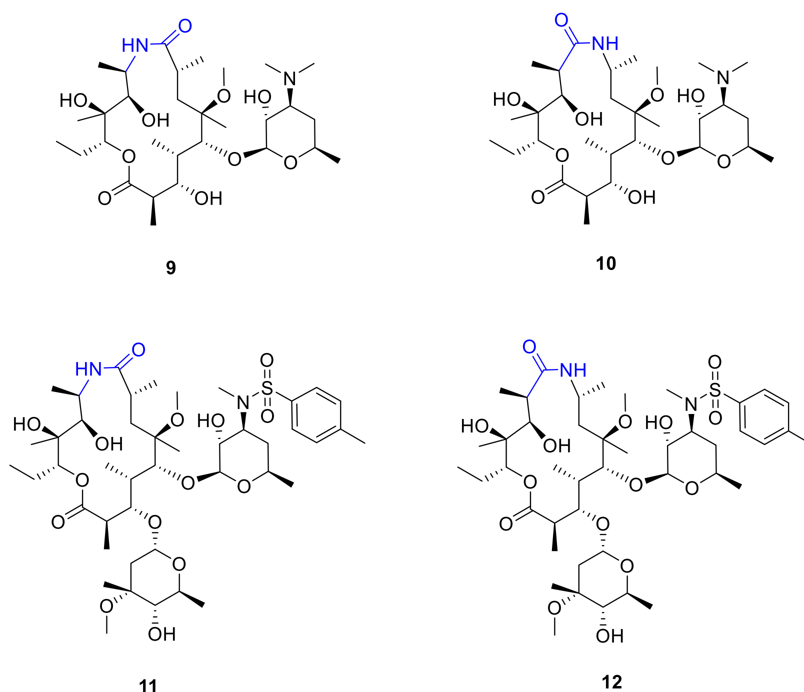

Figure 5. Impurities in the 9a-lactam preparation.

result, it is clear that the amount of (*Z*)-oxime must be controlled to <1.2% to get a minimal level (<0.10%) of regioisomer in the lactam.

Subsequently, the optimized process for manufacturing (*E*)-oxime was successfully upscaled.

Scale Up. Further, the optimized oxime formation process was tested on an increased scale.

As indicated in Table 5, a systematic approach was followed for up scaling the developed process. Scale up was initiated on a 5 kg scale (entry no1) in a kilo lab. The obtained results were encouraging, wherein the amount of undesired (*Z*)-oxime was well controlled below or ~1%.

Table 5. Purity Profiles of Scale Up Batches

		HPLC purity of isolated solid (% area)		
entry	batch size of clarithromycin **1** (kg)	oxime **3**	oxime **4**	% yield
1	5	~97	0.9	60
2	~30	~96	0.9	66
3	~40	~96	1.0	66
4	90	~98	1.0	66
5	90	~94	1.1	69

With boosted confidence, further scale-up batches were planned on a 30−40 kg (entries 2 and 3) scale; and to our expectations both the batches worked well on the pilot scale. In both the batches, the amount of (*Z*)-isomer was well controlled to ~1%. Additionally, when two batches (entries 4 and 5) were performed on a 90 kg scale, to our delight the obtained results were quite consistent with those of of 30−40 kg scale batches, with an isolated yield in the range of 60−70%. Therefore, it can be concluded, as no surprises were observed during scaling up and the amount of (*Z*)-oxime was well controlled ~1.1%, that the developed work up process parameters indeed are robust.

The subsequent Beckmann rearrangement was scaled up to a 20 kg scale with the (*E*)-oxime **3** obtained with the optimized process. Ultimately, good quality (purity 98−99%) 9a-lactam **7** was obtained with consistent isolated yields (50−55%) and a precisely controlled (<0.10%) amount of undesired lactam **8**, as shown in Table 6. This confirms that the obtained quality of (*E*)-oxime delivers high-quality 9a-lactam on a significant (20 kg) manufacturing scale as well.

The optimization of the Beckmann rearrangement is not considered in scope for this publication. Nevertheless, optimized conditions are shared in this Article.

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Table 6. Purity Profiles of Representative Scale Up Batches

entry	batch size of oxime **3** (kg)	input of (*E*)-oxime **3** (Table 4) (kg)	HPLC purity of isolated solid (% area) lactam **7**	lactam **8**	% yield
1	10	~30	~98	0.06	50
2	20	~40	~99	0.08	53
3	20	90	~99	0.03	54
4	20	90	~99	0.06	54

■ CONCLUSION

A robust, scalable process was developed to obtain significantly pure (*E*)-oxime of clarithromycin. This entailed development of a simple workup process to remove the undesired (*Z*)-isomer; hence, no additional purification operation was required. Cleavage of acid-sensitive group(s) can be controlled by controlling the pH of the reaction between 7 and 8. Removal of the unwanted isomeric impurities without an additional purification step makes this process economically viable. The product obtained with this process was successfully converted by a Beckmann rearrangement to the desired 9a-lactam up to a 20 kg scale with high purity. This makes isomer-free 9a-lactam readily available for the synthesis of potential APIs derived from this interesting macrolide scaffold.

■ MATERIALS AND METHOD

In the lab, all the developmental experiments were performed in a 500 mL to 2 L glass round-bottom flask equipped with an overhead stirrer and placed in Heidolph oil batch. Kilogram-scale batches were performed in 2000−5000 L capacity pilot scale reactors. Commercial-grade solvents and reagents were used. IP-grade clarithromycin was procured from a domestic supplier. Characterization of impurities was performed by the nuclear magnetic resonance (NMR) technique. Spectra were recorded at room temperature (unless specified otherwise) in solvents such as $CDCl_3$/DMSO-d_6 as appropriate. NMR (^1H and ^{13}C) spectra were recorded on a Bruker Avance Neo 400 MHz spectrometer . Chemical shift values were reported as a ppm with reference to tetramethylsilane. LCMS spectra were acquired on a Shimatzu LCMS8030 instrument with electron ionization (EI) of 70 eV, chemical ionization (CI) of 100 eV, and methane as the reactant gas. High-resolution mass spectra (HRMS) were recorded on an Orbitrap Exploris 120 instrument (Thermofisher) using an X-bridge phenyl 5 μm (250*4.6 mm) column (Waters), a column oven temperature of 30 °C, a flow rate of 0.5 mL/min, and a run time a 30 min using mobile phase A (0.1% formic acid in water) and mobile phase B (0.1% formic acid in acetonitrile). The gradient of mobile phase B was 10% (0−5 min), 80% (6−24 min), and 10% (25−30 min) with ion source type H-ESI.

Reaction conversion and the purity of the isolated solid were monitored on an Agilent-make HPLC with the United States pharmacopeia (USP) method of analysis reported for clarithromycin. HPLC method parameters are as follows: Poroshell C18 (100 × 4.6) mm column, column oven temperature of 40 °C, wavelength of 205 nm, flow rate of 1.1 mL/min, injection volume of 10 μL, and run time of 42 min using mobile phase A (weight about 4.76 g of potassium dihydrogen phosphate in 1 L of water (HPLC grade) adjusted to pH 4.4 with dilute phosphoric acid or potassium hydroxide (45% w/v)) and mobile phase B (acetonitrile).

■ EXPERIMENTAL PROCEDURE

Example 1: Preparation of Clarithromycin 9-(*E*)-Oxime (3). To a solution of hydroxylamine hydrochloride (167.2 kg, 2407 mol, 20 equiv) in methanol (450 L, 5 M) was added sodium acetate trihydrate (327.5 kg, 2406 mol, 20 equiv) at 20 to 30 °C, followed by the addition of sodium bicarbonate (5.05 kg, 60.16 mol, 0.5 equiv) and clarithromycin (90 kg, 120.32 mol, 1 equiv) at 20 to 30 °C. The reaction mixture was heated to 60−70 °C and refluxed under stirring for 20−24 h. The reaction solution was concentrated to a minimum stirrable volume (~1 M) and further diluted with a mixture of dichloromethane (900 L, 10 M) and water (540 L, 6 M). The organic layer was separated and treated with a 10% aq. sodium bicarbonate solution (10 M w.r.t. clarithromycin) to adjust the pH to about 8. The biphasic reaction mixture slurry was filtered (sticky wet cake). From the MLR the clear biphasic filtrate was separated. The organic layer was washed with brine and concentrated under vacuum. Dichloromethane (~3−4M) was added to the concentrated mass, and the mixture was stirred for 30 min at room temperature and filtered. The MLR was concentrated to ~0.5 to 1 residual volume. Isopropyl alcohol (360 L, 4 M) was added to the concentrated organic layer at 40−50 °C and the resulting mass was further concentrated to a minimum stirrable volume (~1−2 M). The resultant mixture was heated to 80−85 °C for 0−2 h. The reaction mixture was cooled gradually to 0−10 °C under stirring, and the solid was filtered and washed with isopropyl alcohol. The wet solid was dried to obtain clarithromycin 9-(*E*)-oxime (59.4 kg, 64.70% yield) with an HPLC purity of 97.49% and clarithromycin 9-(*Z*)-oxime with a purity of 0.97%.

Example 2: Isolation and Purification of Clarithromycin 9-(*Z*)-Oxime (4). The sticky wet cake obtained during the work up operation described in example 1 from several lab batches was triturated with 4 M DCM three times. The solid was filtered and dried to obtain 20 g of 9-(*Z*)-oxime (HPLC purity: 94.39%).

Example 3: Synthesis of Decladinosylated Clarithromycin 9-(*E*)-Oxime (5). To a solution of 2 N aq. HCl (5M) in 5 M water was charged 15 g of clarithromycin 9-(*E*)-oxime in one lot. The resultant slurry was stirred at 20−30 °C for 24 h. The reaction progress was monitored by TLC. After complete consumption of 9-(*E*)-oxime, the slurry was filtered and suck dried for 2−3 h. Further crude was purified by column chromatography using 100−200 mesh silica gel and ethyl acetate/hexane as a mobile phase, and 7.2 g of dry solid was obtained (HPLC purity: 95.49%).

Example 4: Synthesis of Decladinosylated Clarithromycin 9-(*Z*)-Oxime (6). This compound was prepared from clarithromycin 9-(*Z*)-oxime on a 10 g scale using the same procedure as followed in example 3. Pure solid (~7 g) was obtained after column chromatography (HPLC purity: 94.73%).

Example 5: Preparation of 9a-Lactam (7) through Beckmann Rearrangement. To a solution of 9-(*E*)-oxime (20 kg, 26.21 mol, 1 equiv) in acetone (100 L, 5 M) was added a solution of *p*-TsCl (7.745 kg, 40.62 mol, 1.55 equiv) at −25 to −20 °C over a period of 10−20 min, followed by the addition of aq. sodium bicarbonate (4.63 kg, 55.04 mol, 2.1 equiv) over a period of 1 to 2 h at −25 to 0 °C. Upon the complete addition of base, the reaction mixture was gradually warmed to 20−25 °C over a period of 2−3 h. The resultant

reaction mixture was stirred for 1 h. After the completion of the reaction, the mass was basified using 1 M aq. KOH at 10−15 °C. The solvent was removed by distillation. The residue thus obtained was saturated with a brine solution, and the product was extracted in DCM. The crude solid was isolated by removing the solvent, followed by chasing with *n*-heptane and filtration. Purification of the crude with a mixture of IPA and heptane provided pure wet 9a-lactam. The wet material was dried at 45−50 °C at 5−15 Torr vacuum to obtain 12.3 kg (61.5% yield)of the desired 9a-lactam (HPLC purity: ∼99.1%; undesired lactam isomer: ∼0.06%).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c08207.

^{1}H NMR and ^{13}CMR spectra and data, HPLC retention times/relative retention time of compounds **1−12**, LCMS data for compound **3−4**, and HRMS data for compounds **5−12** (PDF)

■ AUTHOR INFORMATION

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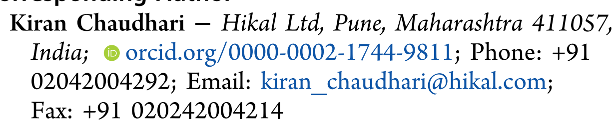

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Notes

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■ ABBREVIATIONS

APIs active pharmaceutical ingredients
aq aqueous
CLR clarithromycin
DCM dichloromethane
EP European pharmacopeia
Eq equivalent
HPLC high-performance liquid chromatography
IPA isopropyl alcohol/2-propanol
kg kilogram
L liter
LCMS liquid chromatography mass spectrometry
MHz megahertz
MLR mother liquor
MTBE methyl tertiary butyl ether
no. number
°C degree Celsius
ppm parts per million
p-TsCl *para*-toluene sulfonyl chloride
RM raw material
USP United States pharmacopeia
V volume

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