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A Facile, One-Pot Synthesis of Lacidipine Using in Situ Generation of Wittig Intermediates†

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Abstract:

An improved, one-pot process for the preparation of lacidipine (1) via an efficient in situ generation of Wittig intermediates is reported. Generation of ylide (4) by dehydrobromination of phosphonium salt (3) followed by in situ condensation of 4 with *o*-phthalaldehyde (5) to yield corresponding olefin (6) and its subsequent reaction with crotonate derivative (7) in the same pot furnished the drug substance 1 with an overall yield of about 51% over the reported yield of about 24% starting from the corresponding ylide. The present work overcomes the challenges associated with prior art processes such as chromatographic purifications, handling of unstable intermediates, and formation of byproducts as potential impurities. The interesting insights on the safety aspects of the process, drawn through calorimetric studies, rendered the successful implementation of the process at manufacturing facility.

Introduction

(*E*)-4-[2-[3-(1,1-Dimethylethoxy)-3-oxo-1-propenyl]phenyl]-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester[1] (lacidipine, **1**), a vascular-selective calcium antagonist with a potent and long-lasting antihypertensive activity is marketed under the brand names, Lacipil and Motens.[2] The first reported synthesis[3] of **1** involved the reaction of ylide[4] **4** with *o*-phthalaldehyde **5** in dichloromethane to give crude olefin **6** as yellow oil, which was purified by column chromatography using petroleum ether and diethyl ether before it was reacted with amino crotonate **7** in ethanol in the presence of trifluoroacetic acid at −10 °C for 1.5 h. Quenching the mass into an aqueous solution of sodium bicarbonate and extracting **1** in *tert*-butyl methyl ether, concentration of the organic layer, and subsequent trituration of the obtained oil with petroleum ether gave crude lacidipine, which was crystallized to give pure **1** with an overall yield of 23.7% (starting from **4,** Scheme. 1). Alternatively, condensation of **6** and **7** in acetic acid at room temperature followed by column chromatography purification provided compound **1** with an overall yield of 5.4% (starting from **4**).

The challenges encountered while following this reported process were: (a) handling of unstable Wittig intermediate **4**, (b) formation of potential impurities such as vinyl benzaldehyde (**6a**) and dimer (**6b**), (c) classical problem of removing the byproduct Ph_3PO (**6c**), (d) use of column chromatography for isolation and purification, and (e) low overall yield (about 24%). The reported procedures as described above are either lengthy or used hazardous and/or relatively expensive chemicals.[3] Herein, we report an improved, facile, and one-pot process for the preparation of **1** by surmounting the aforesaid challenges. Our approach was aimed to avoid the isolation and purification of critical intermediates **4** and **6** by designing ylide generation, olefination, and condensation with amino crotonate **7** in single pot. In this new process, the potential impurities, byproduct, and unreacted intermediates are efficiently controlled through proper understanding of process parameters responsible for impurity formation coupled with an efficient workup process. The process was scaled up successfully by assessing the process safety of optimized process through reaction calorimetry.

Results and Discussion

Identification of Challenges in the Process Development of 1 Using the Reported Synthesis (Scheme 1). Phosphonium bromide[5] (**3**) when treated with an aqueous solution of sodium hydroxide, underwent rapid dehydrobromination to yield ylide **4** along with the formation of impurities due to its instability under the reaction conditions. It was also observed that subsequent reaction of **4** with **5** led to the predominant formation of decarboxylated impurity **3a**, which in turn will further react with **5**, resulting in vinylbenzaldehye (**6a**) as an impurity. Formation of dimer **6b** is attributed to a lack of chemoselectivity as there are two equivalent formyl groups present in *o*-phthalaldehyde **5**. The dimer impurity **6b** was independently synthesized by reacting **5** with an excess of **3** in the presence of sodium hydroxide using dichloromethane or 1,4-dioxane as

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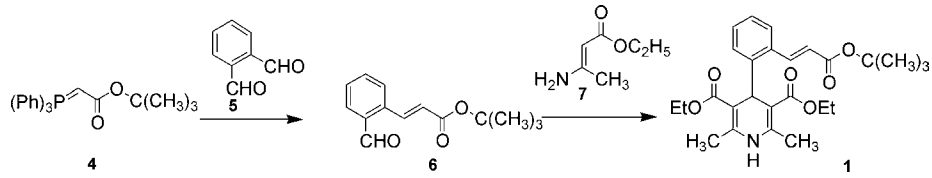
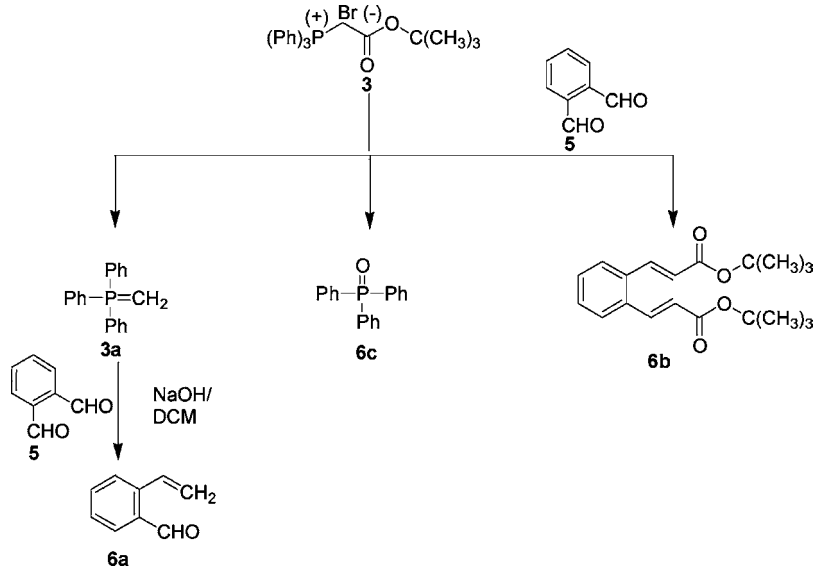
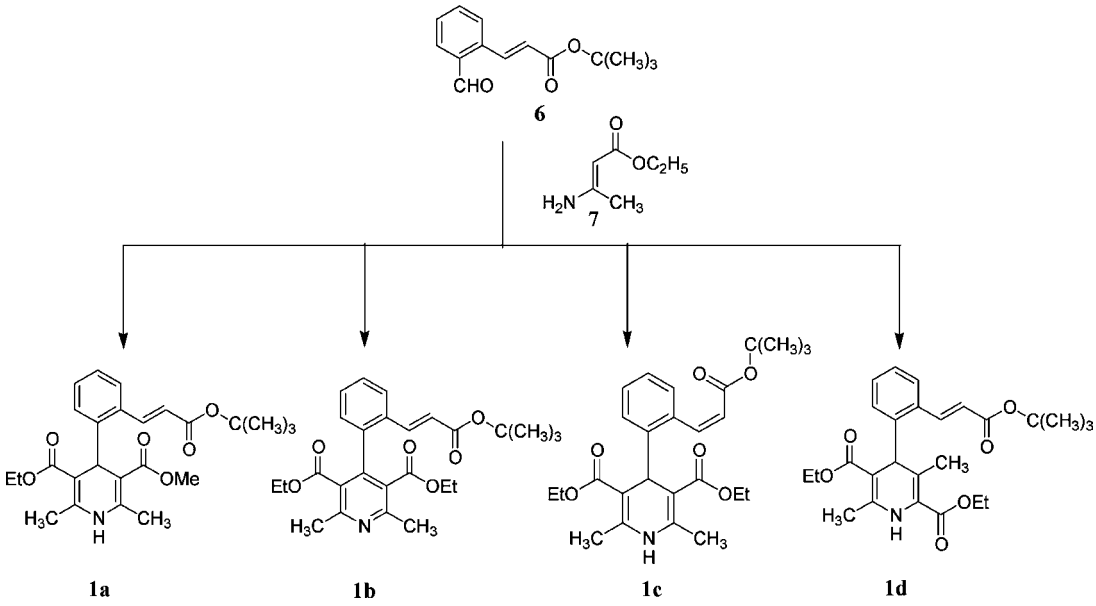
Scheme 1. **Synthetic scheme for lacidipine (1)**



Scheme 2. **Formation of impurities 6a, 6b, and 6c**



Scheme 3. **Formation of impurities 1a, 1b, 1c, and 1d**



a solvent.[6] The synthesized sample of **6b** was characterized using spectroscopic analysis and was found to be identical with the impurity isolated from the reaction of **4** with **5** (Scheme 2).

Reaction of benzaldehyde derivative **6** with aminocrotonate **7** following the known process led to the formation of another set of impurities characterized as ethyl methyl carboxylate (**1a**), pyridine dicarboxylate (**1b**), *z*-isomer (**1c**) and regio isomer (**1d**).[6] Impurities **1a**, **1b**, and **1c** were earlier reported as impurities of lacidipine in British Pharmacopoeia,[7] whereas **1d** was a new impurity, whose formation may be attributed to the lack of regioselectivity during the reaction (Scheme 3). Interestingly, compound **1** obtained from the condensation of **6** with **7** in acetic acid at 25−30 °C, was found to contain the major amount of **1d**, while the same reaction performed in ethanol in the presence of trifluoroacetic acid led to a very smaller amount

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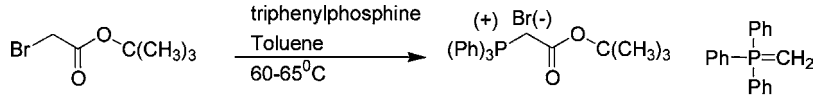
(8) Reaction completion was monitored by thin layer chromatography for the absence of corresponding phosphonium salt and ylide (approximately 0.2 and 0.1 retention factors, respectively, using 15% methanol in chloroform as mobile phase).

Scheme 4. **Synthesis of phoshoniumbromide (3)**



2 **3** **3a**

Table 1. **Effect of reaction time on the formation of impurity 3a**

reaction time (h)	**3a** (%) by HPLC
3	0.720
6	0.900
12	1.640
18	2.540
24	2.890

Table 2. **Effect of temperature on impurity 1d**

entry	°C[a]	**1d**[b] (%)
1	−15 to −10	0.49
2	−10 to −5	0.50
3	−5 to 0	0.62
4	0 to 5	9.8
5	25 to 35	30.4

[a] Reaction temperature. [b] Regioimpurity by HPLC.

of **1d**. This observation revealed the importance of both Lewis acid and temperature to control regioisomer **1d** in the disclosed process.

Having understood the challenges associated with the reported process, our quest towards designing the process comprises (a) preparing phosphoniumbromide salt **3** in pure form, (b) avoiding isolation of unstable ylide **4**, (c) designing the reaction in a single pot, wherein generation of **4** and its subsequent reaction with the carbonyl compound **5** happen in a tandem manner to provide **6**, and (d) developing a workup process to eliminate critical impurities in **6** before it is condensed with **7** in the same pot to furnish substantially pure **1**.

Process for the Preparation of 3. Our first attempt was aimed to establish a suitable process for the preparation of key starting material **3**. The process for the preparation of **3** involved the reaction of triphenylphosphine with *ter*-butylbromoacetate (**2**) in toluene at 60−65 °C for 4−5 h. Usual workup followed by drying under vacuum at 65−70 °C provided compound **3** in 95% yield with 99.3% purity by HPLC. Traces of triphenylphosphine present in the compound **3** were efficiently removed by toluene washings. During optimization, under abuse studies when the reaction was maintained for more than 20 h to evaluate the impact of reaction time, the formation of **3a** (Scheme 4) was observed (Table 1). The content of this impurity was a function of reaction time, and preferred maintenance time to control the formation of this impurity was 4−5 h.

Preparation of Lacidipine (1). Having pure **3** in hand, our next endeavor was to design a robust process for lacidipine (**1**). As per our design (Scheme 5), the process for the formation of **1** in a single pot was performed as follows: aqueous solution of sodium hydroxide was added slowly to the mixture of **3** and **5** in dichloromethane at −5 °C, wherein generation of ylide **4** and its subsequent reaction with *o*-phthalaldehyde **5** in the same pot in a tandem manner led to the formation of **6** within 30−40 min, and complete conversion of **3** and **4** was monitored by TLC[8]. After completion of the reaction, the organic layer was concentrated, and the resultant crude was treated with *n*-heptane. The byproduct (triphenylphosphine oxide, **6c**) separated in *n*-heptane was removed by filtration, and the filtrate was concentrated to get the olefin **6** as syrup. This syrup was diluted with isopropanol, a solution of **7** in isopropanol and trifluoroacetic acid were added successively at −10 °C, and the reaction mass was stirred at −10 °C until reaction completion, monitored by TLC. Reaction mass was quenched over sodium bicarbonate solution, and the product was extracted with ethylacetate at pH 7.0−8.0. Finally, the organic layer was concentrated, and product **1** was isolated in the pure form from isopropyl alcohol.

In this reaction, the mole ratio of compounds **3** and **5** and also the reaction temperature were key factors in influencing chemoselectivity. Thus, the mole ratio of 1:1.4 with respect to compounds **3** and **5** and the reaction temperature of −5 to 0 °C were found to be ideal in achieving a high degree of chemoselectivity, minimizing the formation of impurity **6b** in the reaction.

Also, the quantity of NaOH had a profound effect on reaction completion and in the removal of unreacted **5** in view of its high solubility in alkali. Duration of NaOH addition to a mixture of **3** and **5** under controlled temperature to facilitate the tandem reaction in the reaction pot was also a critical parameter in the process.

Further challenge was to remove the byproduct **6c** formed during Wittig olefination.[9]

The difference between the solubilities of **6** and **6c** in heptane was exploited to obtain compound **6** free from **6c**. Thus, the syrup containing **6** and byproduct **6c** was taken in heptane at ambient temperature, and undissolved **6c** was removed by filtration, and the filtrate was concentrated to get pure **6**.

In the condensation reaction of olefin **6** with amino crotonate **7** to provide lacidipine **1**, reaction medium and temperature have significant impact on the purity of **1**. Solvent-screening studies indicated that isopropanol was an ideal solvent to access **1** with better purity. Content of impurity **1d** increased with reaction temperature (Table 2), and it was about 30% at 35 °C. Based on optimization studies, −10 to −5 °C reaction temperature, 3 mol equiv of **7**, and 2.25 mol equiv of trifluoroacetic acid (TFA) were finalized for this stage.

Furthermore, for an in situ process, carryover of earlier stage raw materials, reagents, intermediates, byproducts, side reaction products, and catalysts into the isolated product is the commonly observed phenomenon. In our process, there was the possibility of 12 such impurities to be present in the product. Among them two (**5** and **7**) were key starting materials, eight (**3a**, **6a**, **6b**, **1a**, **1c**, **1d**, **3**, and **6**) were process-related impurities, one (**1b**) was a degradation product, and one (**6c**) was a byproduct. In

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Scheme 5. **Improved one-pot synthetic scheme for lacidipine (1)**

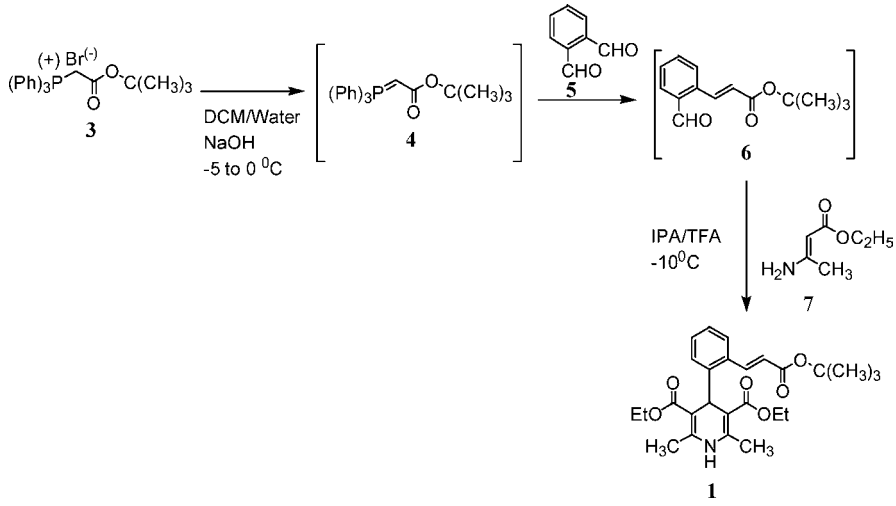

Table 3. **Measured solubility of 3, 5, and 1 in ICH class 3 solvents**

	solvent[a]								
cmpd	acetone	EtOAc	DMSO	EMK	IPA	*tert*-BuOH	EtOH	MIK	TBME
3	++++	++	++	++	++	++	++	++++	++++
5	+	+	+	+	++	+	+	+	++
1	+	++	+	++	++++	+++	+++	+++	+++

[a] EtOAc = ethylacetate, EMK = ethylmethyl ketone, IPA = isopropanol, *tert*-BuOH = tertiary butanol, EtOH = ethanol, MIK = methylisobutyl ketone, TBME = tertiary butyl methyl ether; + = freely soluble (1−10 times), + + = soluble (10−30 times), + + + = sparingly soluble (30−100 times), + + + + = slightly soluble (100−1000 times).

Table 4. **Measured solubilities of 6b, 6c, 1d and 1 in isopropanol**

cmpd	description[a]	solubility
6b	++	1 g is soluble in 30 volumes/mL
6c	+	1 g is soluble in 3 volumes/mL
1d	+++	1 g is soluble in 60 volumes/mL
1	++++	1gm is soluble in 130 volumes/mL

[a] + = freely soluble (1−10 times), + + = soluble (10−30 times), + + + = sparingly soluble (30−100 times), + + + + = slightly soluble (100−1000 times).

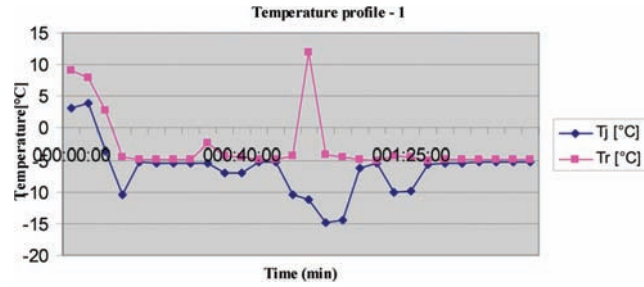

Figure 1

the light of these observations, we have developed an appropriate workup process addressing all of these impurities. The workup process involved quenching of the reaction mass over sodium bicarbonate solution to neutralize unreacted TFA and adjusting the reaction mass pH to 7.0−8.0 and extracting the pure product (**1**) into ethyl acetate by leaving the impurities and unreacted **7** in the aqueous layer.

In order to identify a suitable solvent for crystallization, we have measured isothermal solubilities of compounds **3**, **5**, and **1** in selected ICH class III solvents (Table 3) and used those solvents for purification.

These studies revealed that, isopropanol was an apt solvent, which was further supported by the solubility data generated for **6b**, **6c and 1d** (Table 4).

On the basis of this study, the crude **1** was crystallized from isopropanol, which involved dissolution of crude **1** in isopropanol at reflux followed by cooling to 0−5 °C and isolation at the same temperature. The optimal isolation temperature was 0−5 °C. Drug substance **1** crystallized from isopropanol was substantially free of impurities. The levels of 12 identified and other unidentified impurities were very much within the control of single isolation using isopropanol in all the plant production batches, and the results of the batches produced at various scales are depicted in Table 5.

Process Safety Assessment by Reaction Calorimetry (RC). There was no literature precedent to identify the hazards associated with the manufacturing process of **1**. Thus, an initial reaction calorimetric study[10] was performed in the Mettler-Toledo RC1 reaction calorimeter following the parameters of the optimized process. The key outcomes were essentially used for designing the plant equipment, services, and operations to ensure scalability of the optimized process.

Reaction Calorimetry: Results and Discussion. During the olefination reaction, after introducing both **3** and **5** in a 2 L cylindrical reaction calorimeter equipped with an anchor having 105 mm diameter with 200 rpm, it became apparent from comparison of the batch temperature profile inside the reactor (**Tr**) with the reactor jacket temperature profile (**Tj**) during

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Table 5. **Results of the batches at various scales**

	purity by HPLC (%)												
batch input (kg)	**1**[a]	**1a**[a]	**1b**[a]	**1c**[a]	**3a**[b]	**6a**[c]	**6b**[c]	**1d**[c]	**6c**[b]	**3**[b]	**6**[b]	**5**[d]	**7**[d]
0.1	99.92	0.02	0.001	0.028	ND	ND	0.024	0.007	0.019	0.019	ND	0.005	0.006
0.1	99.92	0.005	0.002	0.028	ND	0.001	0.092	0.057	0.078	0.007	ND	0.01	0.018
5.0	99.89	0.03	ND	0.01	ND	ND	ND	0.02	ND	ND	ND	0.04	0.01
5.0	99.75	0.02	0.03	0.07	0.002	ND	0.02	0.05	0.03	0.01	0.02	0.02	0.01
5.0	99.86	0.01	0.002	0.08	ND	ND	0.01	0.07	0.02	ND	ND	ND	0.008

[a] = estimated by HPLC method 1. [b] = estimated by HPLC method 2. [c] = estimated by HPLC method 3. [d] = estimated by GC.

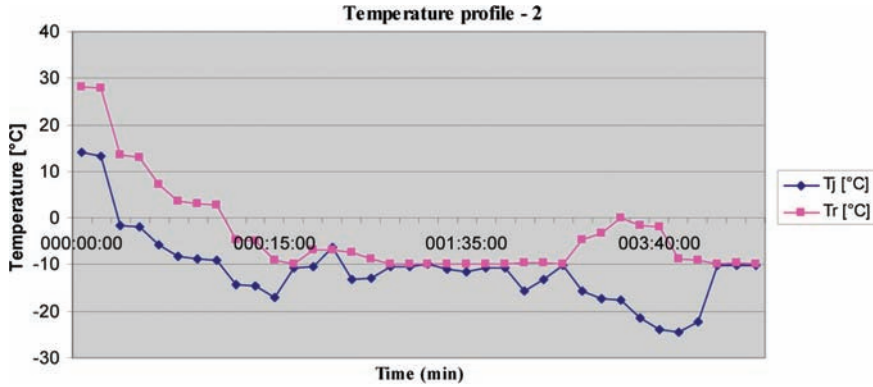

Figure 2

aqueous NaOH solution addition that the estimated adiabatic temperature rise would be 55.6 °C (Figure 1) for a batch size of 100 g of **3** and hence in case of cooling jacket failure at an instant of time during aqueous NaOH solution addition, the reaction mass temperature would rise to 55.6 °C from the operating temperature (−5 °C).

During the condensation of compounds **6** and **7**, when TFA was added to the reaction mass, the estimated adiabatic temperature (T_{ad}) rise was found to be 10.17 °C for a batch size of 75 g of **6**. The most observable occurrence took place during the workup stage. After completion of the reaction, while adding aqueous sodium bicarbonate solution (3.75 mL per min) to the reaction mass in isothermal mode at −10 °C, it was found to be instantaneous with heat evolution, and reaction mass temperature rose to 0 °C at the start of addition, as evidenced by the significant deviation between **Tr** and **Tj** (Figure 2), while the jacket temperature **Tj** dipped to −24.6 °C to maintain the reaction temperature set point of −10 °C. **U** value of the reaction mass after decomposition was found to be decreasing significantly which was an indication of the decreasing heat transfer capability of the reaction mass. Adiabatic temperature rise was found to be 73 °C. Hence, in case of cooling jacket failure at any instant of time during sodium bicarbonate solution addition, the reaction mass temperature would rise by 73 °C from an operating temperature of −10 °C.

Out of three in situ additions and decomposition reactions, it was therefore important to ensure a maximum cooling capacity requirement in the decomposition step, and this process safety assessment data served as the basis for safe scale-up design and successful execution for the optimized process at plant scale.

Experimental Section

The ESI mass spectrum was recorded on 4000-Q-trap LC-mass spectrometer. The FT-IR spectrum was recorded on Perkin-Elmer model spectrum GX series FT-IR as KBr pellet. The ^{1}H NMR spectra were recorded at 400 MHz on Varian mercury plus 400 MHz spectrometer. The chemical shift values were reported on δ scale in ppm with respect to TMS (δ 0.00 ppm) as an internal standard.

Preparation of *tert*-Butoxycarbonylmethyl Triphenyl Phosphoniumbromide (3). A mixture of toluene (32 L) and triphenylphosphine (3.2 kg, 12.1 mol) was heated to 55 °C under nitrogen atmosphere and compound **2** (2.85 kg, 14.6 mol) was added below 60 °C. The mixture was aged for 4 h at 65 °C, product was separated by filtration at ambient temperature under nitrogen atmosphere and dried at 70 °C to yield 5.28 kg (94.63%) of the compound **3**; purity by HPLC 99.31%, MR 172−174 °C. IR (ν_{max}, cm^{-1}) 3052, 3006, 2877, 2831, 2761, 1723, 1587, 1436, 1371, 1138, 1112, 833, 808; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.75−7.9 (m, 15 H), 3.38 (d, 2 H), 1.18 (s, 9 H).

Preparation of Diethyl (*E*)-4-{2-[(*tert*-Butoxycarbonyl)vinyl]phenyl}-1,4-dihydro-2,6-dimethyl pyridine-3,5-dicarboxylate (1). Caustic soda flakes (2.65 kg, 66.25 mol) were dissolved in water (5 L), and this alkaline solution was cooled to ambient temperature and added to a mixture of methylene chloride (20 L), **3** (5 kg, 13.25 mol), and **5** (2.05 kg, 15.29 mol) at −5 °C over a period of 90 min. The reaction mass was aged for about 60 min for completion of the reaction. The organic layer was separated at 30 °C and concentrated under atmospheric pressure until the temperature reached to 55 °C. Then *n*-heptane (35 L) was added to the mass slowly at 55 °C for 40 min. The solvent was stripped off under vacuum below 70 °C, and byproduct **6b** was removed by filtration at ambient temperature after aging for 2 h at the same temperature. Filtrate was concentrated under vacuum below 70 °C, and product was diluted with isopropanol (12.5 L) and cooled to −10 °C.

7 (4.25 kg, 32.92 mol) was dissolved in isopropanol (12.5 L) and cooled to 25 °C. This compound solution was added to

6 at −10 °C in 45 min. TFA (2.8 kg, 22.47 mol) was added at −10 °C in 1 h. Reaction mass was maintained at −10 °C for the completion of the reaction. Sodium bicarbonate (2.6 kg, 30.95 mol) was dissolved in water (50 L), and this solution was added to the reaction mass at 0 °C over a period of about 45 min until the pH reached 7.0−8.0, and then ethylacetate (25 L) was charged. Layers were separated at 30 °C, the aqueous layer was extracted with ethylacetate (12.5 L), and the combined organic layers were concentrated at atmospheric pressure until reaction mass temperature reached 88 °C. Isopropanol (6.3 L) was charged, and the mixture was heated to 75 °C to get a clear solution. Solution was cooled to 0−5 °C, and the product was filtered and dried to furnish pure lacidipine, **1** (2.6 kg, 52.2%) with 99.8% purity by HPLC which melts at 174 °C. IR (ν_{max}, cm^{-1}) 3350, 2980, 2934, 1703, 1676, 1452, 1369, 1311, 1193, 832, 745; ^{1}H NMR (DMSO-d_6, 200 MHz) δ: 8.82 (s, 1 H), 5.20 (s, 1 H), 7.58 (d, 1 H), 7.32 (t, 1 H), 7.12 (t, 1 H), 7.32 (d, 1 H), 3.77 (m, 2 H), 1.05 (t, 3 H), 2.25 (s, 3 H), 8.38 (d, 1 H), 6.32 (d, 1 H), 1.49 (s, 3 H).

Conclusion

In conclusion, an improved, cost-viable, and plant-friendly process was developed for the synthesis of lacidipine, **1**, through in situ generation of the ylide **4** and subsequent condensation with carbonyl compound **5** in a tandem manner in one pot. Thorough understanding of the process parameters coupled with integrated calorimetric approach ensured successful scale-up of the optimized process.

Acknowledgment

We thank the management of the Dr.Reddy's Laboratories Ltd. for supporting this work. Co-operation from the colleagues from analytical research and development is highly appreciated.

Supporting Information Available

Further experimental details and additional information on the work. This material is available free of charge via the Internet at http://pubs.acs.org.

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