Organic Process Research & Development

Communication

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Development of an Improved and Scalable Process for 2-(5-Ethylpyridin-2-yl)ethan-1-ol: Solvent-Free Reaction and Recycling of the Starting Material 5-Ethyl-2-picoline†

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ABSTRACT: The main objective of this exercise was to develop a more efficient process for 2-(5-ethylpyridin-2-yl)ethan-1-ol (**1**), which is the key intermediate in the synthesis of pioglitazone hydrochloride. This process not only features the yield improvement of (**1**) by optimizing reaction variables in solvent-free conditions but also highlights improving the mass efficiency of 5-ethyl-2-picoline (**2**), thereby reducing the effluent load per kilogram of the intermediate.

INTRODUCTION

Pioglitazone HCl[1] chemically known as 5-(4-(2-(5-ethyl-pyridin-2-yl)ethoxy)benzyl)thiazolidine-2,4-dione hydrochloride is used for the chronic management of diabetes mellitus type-2.[2] Most of the drugs within this class went off the therapeutic armamentarium; however, pioglitazone is the only molecule in its class where the benefit outweighs the risks, and as a result, it is the only drug available for patients who warrant treatment of a thiazolidine-class of drug.

A thorough literature review and chemical abstract structure search for the synthesis of pioglitazone hydrochloride reveals more than 150 publications, and most of the literature precedent describes 2-(5-ethylpyridin-2-yl)ethan-1-ol (**1**) as an important intermediate[3a−e] in the synthesis of pioglitazone, but there were only two references describing the synthesis of this intermediate.[4,5]

Robert, L. F. et al.[4] describe the synthesis starting with the reaction of 5-ethyl-2-picoline (**2**) with paraformaldehyde in the presence of potassium persulphate and *tert*-butyl catechol as a catalyst in ethanol at 220 °C to afford (**1**) in 21% yield. This process also described 42% recovery of the starting material (**2**) along with the formation of 10% of 5-ethyl-2-vinylpyridine (**3**) as the byproduct. This process was least attractive of all because of the two main reasons; first was the use of potassium persulphate and *tert*-butyl catechol as a catalyst at large scale has its own disadvantages,[6,7] and second was the high reaction temperature and use of chlorinated solvent. Reddy, R. A. et al. from our group[5] discloses a yield of 23% for (**1**), but the main focus of this article was on the pioglitazone process and not on optimizing the process for the synthesis of (**1**). Additional disadvantages of the above two processes are (a) low conversion in the hydroxymethylation step, which is probably due to the decomposition of formaldehyde at high temperature,[8] and (b) recycling of recovered starting material (**2**) was not the part of the process.

In our continued endeavor for developing an efficient and green process, we focused on a process that is not only easily scalable but also includes the recovery and recycling of the 5-ethyl-2-picoline (**2**) in subsequent batches. This approach would make the process more efficient in terms of cost and the amount of waste generated per kilogram of (**1**). The present article describes the development of a scalable process for the synthesis of (**2**) with improved yield at lower reaction temperature. This process is more efficient (compared to the reported routes[4,5]) because of the recycling of (**2**) and also because of the smaller amount of waste generated per kilogram of the (**2**) produced.

RESULTS AND DISCUSSION

The future of industrial processes lies in minimizing the use of the organic solvents and also in the continuous endeavour to use green solvents. This is evident by the fact that there is increased interest in alternative green solvents or in using solvent-free reaction conditions. Water is an ideal green solvent, and it behaves like an organic solvent at higher temperatures and pressures;[8] thus, we planned to exploit this property of water for the hydroxymethylation of (**2**) provided that the aqueous formaldehyde could be used both as reagent and as a solvent.

At first glance, the process described in route-1 (Scheme 1) seems to be better because the reaction mass is homogeneous due to the use of organic solvents (ethanol). However, we decided to optimize the route-2 (Scheme 1) as it would be more attractive for the large-scale hydroxymethylation of **2** as the reaction could be done in commercially available aqueous formaldehyde itself. To explore the full possibility and usefulness of the process, formaldehyde equivalence, reaction temperature and reaction maintenance time on product conversion and yield were investigated, including recovery and recycle of 5-ethyl-2-picoline (2).

We investigated the process similar to that described by Reddy, R. A. et al.[5] and co-workers. This reaction was performed in an autoclave and after three hours of maintenance, samples were analyzed by GC to determine the conversion. The crude reaction mass composition was

Received: July 21, 2013
Published: December 23, 2013

   dx.doi.org/10.1021/op400196y | *Org. Process Res. Dev.* 2014, 18, 168−173

Scheme 1. Reported manufacturing synthetic route to 2-(5-ethylpyridin-2-yl)ethan-1-ol (1)[9]

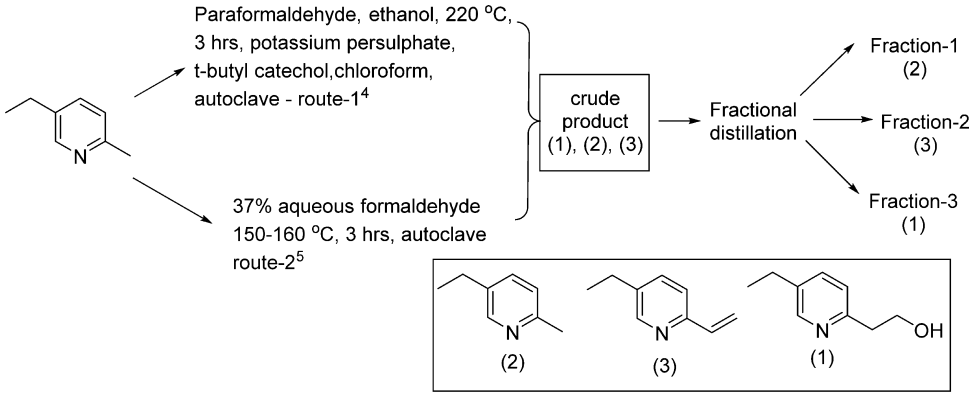
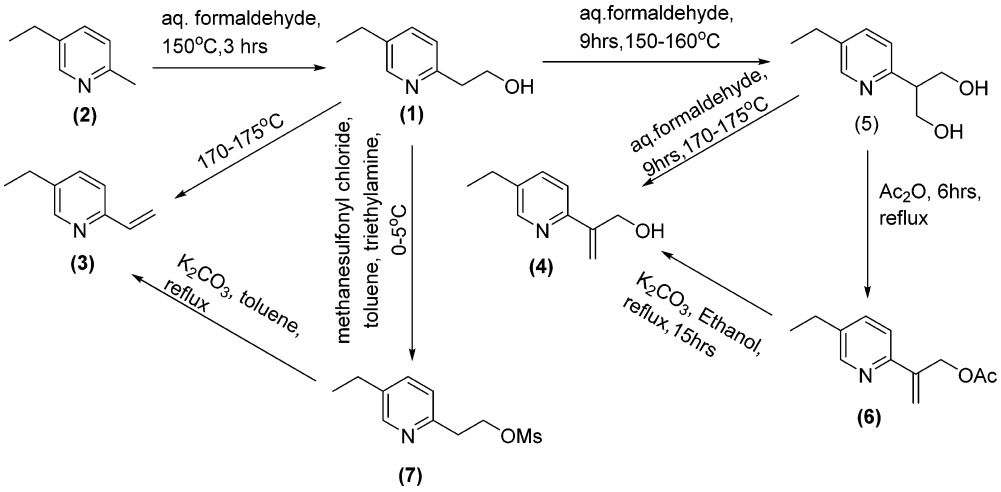


Table 1. Effect of time on the hydroxymethylation of (2) using the procedure of route-2[5]

entry	formalin (equiv)	temp.[a] (°C)	time[b] (min)	pressure[c] (kg/cm^2)	5-ethyl-2-picoline[d] (2)	2-(5-ethylpyridin-2-yl)-ethan-1-ol[e] (1)
1	1.0	150−160	60	5.0−6.0	86.8	8.3
2	1.0	150−160	120	5.0−6.0	78.6	15.5
3	1.0	150−160	180	5.0−6.0	70.2	24.5
4	1.0	150−160	240	5.0−6.0	70.6	25.1
5	1.0	150−160	300	5.0−6.0	68.4	25.0
6	1.0	150−160	360	5.0−6.0	67.5	25.8
7	1.0	150−160	420	5.0−6.0	66.5	26.5

[a]Reaction temperature. [b]Reaction time. [c]Autoclave pressure. [d]Starting material. [e]Product composition of the reaction mass by GC (% area).

Scheme 2. Structures of impurities (2), (3), (4), and (5) along with their synthetic routes



determined by gas chromatography (GC) with respect to the time as shown in Table 1.

It was observed (Table 1) that the reaction becomes sluggish after 5 h at the reaction temperature of 150−160 °C with one equivalent of aqueous formaldehyde. On the basis of this preliminary data, we reasoned that a detailed study was required to understand the effect of reaction time, mole equivalents of formaldehyde, and reaction temperature on the yield. However, before starting the actual optimization work, it was felt important to identify all impurities forming during the reaction.

Impurity Isolation and Characterization. Since the 2-(5-ethylpyridin-2-yl)ethan-1-ol (**1**) was a key intermediate for pioglitazone, its quality (impurity profile) was critical for the subsequent stages in the manufacturing process. In this regard a comprehensive study was carried out for the characterization of these impurities by isolating them and subjecting them to spectral analysis. The structures of these impurities were reconfirmed by their synthesis as described in Scheme 2.

It was observed that, when we reproduced the process described in route-2[5], there were two unknown impurities at ∼1.14 RRT (impurity **4**) and at 1.44 RRT (impurity **5**) apart from two known impurities (**2** and **3**). All four impurities (**2**, **3**, **4**, and **5**) were isolated and characterized. Impurity (**2**)[10] was found to be the unreacted starting material, but the remaining three impurities (**3**), (**4**), and (**5**) were found to be the derivatives of the product (**1**) as shown in Scheme 2. Impurity (**3**), the known impurity was identified as 5-ethyl-2-vinylpyridine,[11] and it formed when product (**1**) was subjected to higher temperature and higher pressure. Addition of second mole of formaldehyde to the product (**1**) gave impurity (**5**) when subjected to longer reaction time. This impurity (**5**)[1a] on

dx.doi.org/10.1021/op400196y | Org. Process Res. Dev. 2014, 18, 168−173

dehydration gave impurity (**4**) as shown in Scheme 2. Impurities (**3**), (**4**), and (**5**) were synthesized in the lab to confirm the structures as shown in Scheme 2 (see the Experimental Section for more details).

Process Optimization. We started the process optimization by taking the process described in route-2 as our benchmark. The first parameter that we considered for the optimization was the equivalents of formaldehyde. The process described in route-2[5] indicated that one equivalent of formaldehyde was the optimum quantity for the best yield, and beyond one equivalent there was an increase in the side reactions. We reasoned that not only the formaldehyde mole equivalents but also the reaction time and temperature could influence the yield. Hence, all variables were studied separately to obtain the optimized process. The reaction was performed in an autoclave, and after reaction maintenance, samples were analyzed by GC to determine the conversion (**% area in GC**) under varied conditions.

Optimization of Formaldehyde Equivalence. We reasoned that increasing the quantity of formaldehyde could be beneficial for increasing the conversion in the hydroxymethylation stage. Hence, the effect of formaldehyde equivalent was studied by following the reaction condition described in route-2 by keeping the reaction time (3 h) and temperature (150−160 °C with autoclave pressure of 5−6 kg/cm^2) constant (reaction was sluggish afterward, see Table 1). It was observed that by increasing the formaldehyde quantity to 1.75 equiv resulted in gradual increase in the formation of product (**1**) along with increasing levels of the impurities (**3**), (**4**), and (**5**). Increasing the formaldehyde quantity beyond 1.75 equiv resulted in a sudden drop in the product concentration with increases in the impurities level (Table 2). Hence, 1.75 equiv of formaldehyde (entry 6, Table 2) was found to be the optimal at a reaction temperature of 150−160 °C with a reaction time of 3 h.

Table 2. Effect of formaldehyde equivalents on reaction composition

		% product **1** and impurity distribution[a]				
entry	formaldehyde (equiv)	**1**	**2**	**3**	**4**	**5**
1	0.5	10.48	88.97	0.15	0.03	0.0
2	0.75	18.43	80.92	0.37	0.03	0.0
3	1.00	17.69	81.54	0.43	0.04	0.0
4	1.25	21.13	76.40	0.58	0.15	1.51
5	1.50	27.61	67.17	0.72	0.28	3.01
6	1.75	36.78	61.59	0.93	0.44	0.04
7	2.00	26.46	68.50	1.18	0.53	0.04

[a]Product (**1**), starting material (**2**), and byproduct (**3**, **4** and **5**) composition of the reaction mass by GC (area normalization).

Optimization of Temperature. After the equivalent of formaldehyde was optimized, we investigated the effect of temperature on the conversion by keeping the equivalents of formaldehyde constant to 1.75 equiv. The reaction was found to be sluggish up to 125 °C; thereafter there was a sudden increase in the conversion to 35.36% at an elevated temperature of 150−155 °C. Further increasing the temperature had no effect on conversion; instead there was an increase in the levels of the impurities (entry 4, Table 3). Hence, temperature of 150−155 °C was taken as the optimal reaction temperature for optimal conversion with minimum impurities.

Optimization of the Reaction Time. The effect of reaction time on the conversion was studied using 1.75 equiv of formaldehyde and a reaction temperature of 150−155 °C (autoclave pressure of 5−6 kg/cm^2). It was observed that there was an increase in the conversion until 180 min (3 h), and thereafter a plateau was observed with increased levels of the impurities (Table 4). Hence, 3 h was taken as an optimal time for the cleaner conversion.

Table 4. Effect of time on the conversion and impurity profile

		% product and impurity distribution[a]				
entry	reaction time (min)	(**1**)	(**2**)	(**3**)	(**4**)	(**5**)
1	60	20.9	78.2	0.54	0.01	0.01
2	120	24.2	74.2	1.05	0.21	0.19
3	180	38.6	55.0	1.59	0.80	0.02
4	240	37.8	47.9	2.10	1.53	0.26
5	300	38.2	42.8	2.30	2.29	0.30

[a]Product **1**, starting material **2** and byproduct (**3**, **4**, and **5**) composition of the reaction mass by GC (area normalization).

Process Description of Recovering and Recycling of (2). As discussed above, the reaction never went to completion, and there was always a quantity of unreacted starting material (**2**) in the reaction mass. Hence, it became important for us to recover this unreacted (**2**) and also to establish its recycling procedure in subsequent batches. With optimized reaction conditions as described above (1.75 equiv of aqueous formaldehyde, reaction temperature of 150−155 °C and reaction time of 3 h) a few reactions were executed in lab. After the reaction went to completion (36−38% conversion), the reaction mass was cooled and subjected to vacuum fractional distillation. Fraction-1 contains unreacted (**2**) and water, water was separated, and (**2**) was analyzed by GC for quality followed by its recycling into the subsequent batch (Figure 1, also see Table 5). Fraction-2 contains impurity (**3**), and the last fraction-3 contains the desired product (**1**) as shown in Figure 2.

Once the recycling process for (**2**) was established and optimized, it became imperative for us to compare the current

Table 3. Effect of temperature on the impurity profile of (1)

			% product and impurity distribution[a]				
entry	reaction temperature (°C)	autoclave pressure (kg/cm^2)	(**1**)	(**2**)	(**3**)	(**4**)	(**5**)
1	100−105	0.7	7.58	91.97	0.0	0.0	0.0
2	120−125	1.5	7.01	92.54	0.18	0.0	0.0
3	150−155	6.0	35.36	62.69	0.89	0.56	0.278
4	170−175	8.0	34.25	51.40	6.62	7.40	0.039

[a]Product (**1**), starting material (**2**), and byproduct (**3**, **4**, and **5**) composition of the reaction mass by GC (area normalization).

dx.doi.org/10.1021/op400196y | *Org. Process Res. Dev.* 2014, 18, 168−173

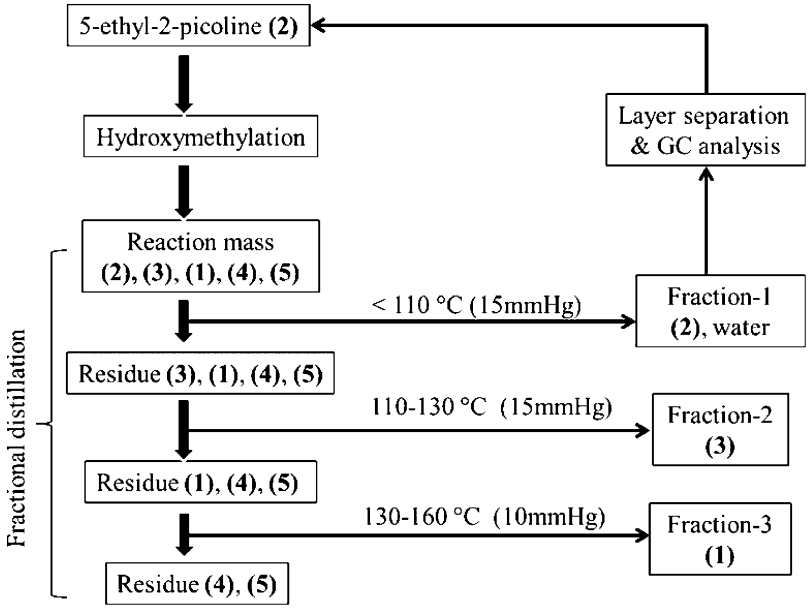


Figure 1. Recovery and recycling of (2) from fraction-1.

Table 5. Comparison of the reported process[5] and the present process with two times recycling of (2)

	quantity of **2** (g)						fraction-3 purity[d]					
entry	recycle	fresh	recovered	formaldehyde[a] equiv	temp[b] (°C)	time[c] (h)	(1)	(2)	(3)	(4)	(5)	fraction-3 (g)
present process route-2r[5]												
1		200	0	1.0	150−155	3	98.5	0.27	0.02	0.29	ND	52.0
2	1st	90	**110**	1.0	150−155	3	98.6	0.08	0.07	0.48	ND	51.5
3	2nd	91	**109**	1.0	150−155	3	98.4	0.12	0.05	0.53	ND	48.5
optimized process route-3												
4		200	0	1.75	150−155	3	96.3	0.94	0.62	0.97	ND	70
5	1st	98	**102**	1.75	150−155	3	96.28	0.95	0.60	0.98	ND	68.5
6	2nd	95	**105**	1.75	150−155	3	96.33	0.93	0.61	0.97	ND	68

[a]Formaldehyde mol equiv. [b]Reaction temperature. [c]Reaction time (in hours). [d]Determined by GC.

Table 6. Effluent load comparison[m]

	a (g)	*b* (g)	*c* (g)	*d* (g)	*e* (g)	*f* = *a*−*e* (g)	*g* (g)	*h* = *f*−*g* (g)	*i* (g)	*j* = *b*−*i* (g)	*k* = *c*+*h*+*j* (g)	*l* (kg)
route-1[4]	**200**	49.63	267.5	**57**	**84.2**	115.8	45.68	70.1	11.3	38.3	375.9	**6595.3**
route-2[5]	**200**	49.56	0	**51**	**0**	200	40.87	159.1	10.1	39.4	198.6	**3893.3**
route-2r[5]	**200**	49.56	0	**51**	**110**	90	40.87	49.1	10.1	39.4	88.6	**1736.6**
route-3	**200**	86.73	0	**70**	**105**	95	56.10	38.9	13.9	72.8	111.7	**1596.1**

[a]5-Ethyl-2-methylpyridine (2) input. [b]Formaldehyde (100%) input. [c]Other reagents and organic solvents. [d]Product (1). [e](2) recovered. [f](2) consumed in reaction. [g](2) into (1). [h](2) unused. [i]Formaldehyde reacted. [j]Formaldehyde degraded. [k]Mass generated from 200 g input (1). [l]Mass generated for **1.0 kg** product (1). Route-2 with recovery: **Route-2r**.[5] [m]**MWs**: 5-ethyl-2-methylpyridine (2) **121.18**, formaldehyde **30.03**, 2-(5-ethylpyridin-2-yl)ethan-1-ol (1) **151.21**.

process with the process described in route-2[5] (our benchmark). The main difference between the two processes was the equivalents of formaldehyde and the reaction temperature (see Table 5). In order to have an unbiased and fair comparison of the two processes, both the processes were subjected to recovery and recycling of (2) for calculating yields. In both processes the first batch was taken with fresh (2), whereas the second and third batches were taken with a mixture of recovered and fresh (2) as shown in Table 5. The route-2 process gave a total output of 152 g of the product (1) from three batches of (2) of 200 g each. Out of the 600 g of (2) that was used in three batches, only 381 g of fresh (2) was used, and the rest of it came from recovered (2). On the other hand the current optimized process with 1.75 equiv of formaldehyde gave 206.5 g of (1) utilizing 393 g of fresh (2) as described in Table 5. This clearly indicates the advantage of the current optimized process over route-2 process with respect to the yield.

On the basis of the above information we have evaluated the plant productivity and found that there was a 27% reduction in the consumption of (2), and the number of batches required to meet the production target was reduced by 27%.

Effluent Load Comparison. After the process was optimized and found to be performing to our satisfaction, the

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next challenge was to show the advantage in the terms of the effluent load generated per kilogram of the intermediate (**1**) produced by the current process. This comparison was very much required for making any commercial decision. In order to have an idea of the effluent load, all four processes (references 4 5, with and without recovery, and the current process) were compared for the waste generated per kilogram of (**1**), and data are captured in Table 6. Total effluent generated by the present route (route-3) is 75% less than route-1[4], 59% less than route-2[5] and 8% less than route-2r.[5]

CONCLUSIONS

The present article describes the development of a process for the manufacturing of 2-(5-ethylpyridin-2-yl)ethan-1-ol. The process was improved by exploiting the physical characteristics of the aqueous formaldehyde which allowed us to perform the reaction in the aqueous formaldehyde itself without using any other organic cosolvent. Recovering and recycling of unreacted starting material (**2**) enabled us to increase the efficiency further with decreased effluent load. The current process enabled us to increase the overall productivity by 27%.

Experimental Section. Chemicals and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin layer chromatography (TLC) was performed on E-Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellet with Perkin-Elmer Spectrum GX FTIR instrument, and only diagnostic and/or intense peaks are reported. ^{1}H NMR spectra were recorded in $CDCl_3$ with a Varian Mercury plus 200 MHz instrument. Signals due to the solvent served as the internal standard. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. Mass spectra were recorded with a PE Sciex model API 3000 instrument.

2-(5-Ethylpyridin-2-yl)ethan-1-ol (1). To 1000 mL steel autoclave was added an aqueous solution of formaldehyde (86.73 g on 100% basis) and 5-ethyl-2-methylpyridine (200 g) at room temperature. The temperature was raised to 155 °C over a period of one hour. The resultant reaction mass was maintained at the same temperature for 3 h. The reaction mass was cooled to room temperature, and the contents were transferred into a fractional distillation setup fitted with a closely packed Fenske-type column. Three factions were collected under reduced pressure using the PIG adapter. 5-Ethyl-2-methylpyridine (102 g) was collected as fraction-1 below 110 °C (15 Torr), 5-ethyl-2-vinylpyridine (3−4 g), as fraction-2 between 110 and 130 °C (15 Torr), and 2-(5-ethylpyridin-2-yl)ethan-1-ol (70 g) as fraction-3 below 160 °C (10 Torr).

Found mass (M + H): 152, ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 8.3−7.0 (m, 3H), 4.5 (s, 1H), 4.0 (t, 2H, J = 5.6), 3.0 (t, 2H, J = 5.6), 2.6 (q, 2H, J = 7.8), 1.2 (t, 3H, J = 7.6). IR (KBr): 3349 (OH), 2663 (aromatic C−H), 1037 (C−O).

2-(5-Ethyl-pyridin-2-yl)-1-propan-1,3-diol (5). To a 1000 mL steel autoclave was added 50 g of (**2**) and 202 g of 37% aqueous formaldehyde, and the temperature was raised to 170−175 °C; the resultant reaction mass was maintained at that temperature for about 10 h. Excess formaldehyde was removed under reduced pressure; crude reaction mixture was dissolved in methanol (∼200 mL), and solvent was removed under vacuum. Chromatography with AcOEt/MeOH 9:1 to 8:2 furnished (**5**) as a white solid, with a yield of 20−27%.

Mass found (M + H): 182, ^{1}H NMR: ($CDCl_3$, 200 MHz): δ 7−8.3 (m, 3H), 4.1 (s, 2H), 4 (m, 4H), 3 (t, 2H, J = 5.6), 2.6 (q, 2H, J = 8), 1.2 (t, 3H, J = 8). IR (KBr): 3349 (alcoholic OH), 2663 (aromatic C−H), 1037 (C−O)

5-Ethyl 2-Vinyl Pyridine (3). Fifty grams of 2-(5-ethyl-pyridine-2-yl)ethanol (**1**) and 37g (1.1 mol equiv) of triethylamine were dissolved in toluene and *p*-toluenesulfonyl chloride (42 g, 1.1 mol equiv) was added slowly at 0−5 °C for about 2−4 h. After that the reaction mass was maintained at 0−5 °C for 30−60 min. The progress of the reaction was monitored by TLC. After the completion of the reaction, the precipitated triethylamine hydrochloride was filtered off to give toluene-4-sulfonic acid-2-(5-ethyl-pyridin-2-yl)ethylester (**7**). This was followed by addition of K_2CO_3 and toluene, and the reaction mass was refluxed for 10 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, salts were filtered, organic layer washed with 25 mL water and the organic layer concentrated under reduced pressure to obtain the title compound (**3**) in 100% yield.

Mass found (M + H): 134; ^{1}H NMR: ($CDCl_3$, 200 MHz): δ = 7.1−8.4 (m, 3H), 6.8 (dd,1H, J = 13.2), 5.6 and 6.1 (dd, 2H, J = 12), 2.6 (q, 2H, J = 7.6), 1.2 (t, 3H, J = 7.6). IR (KBr): 2663 (aromatic C−H), 2966.6 (C−H, aliphatic).

2-(5-Ethylpyridin-2-yl)prop-2-en-1-ol (4). Fifty grams of 2-(5-ethyl-pyridine-2-yl)propane-1,3-diol (**5**) in 85 g (3 mol equiv) of Ac_2O was refluxed for 6 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, Ac_2O was removed under vacuum using a closely packed Fenske-type packing column to give 2-(2-pyridinyl)-3-acetoxypropene (**6**). A solution of (**6**) and K_2CO_3 in ethanol was refluxed for 15 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the reaction mass was concentrated, the resulting solid was extracted with CH_2Cl_2, the solvent was removed under vacuum, and the resulting oil was distilled under reduced pressure (<10 mmHg at 165−170 °C) to obtain the title compound (**4**) in 71% yield.

Mass found (M + H): 162, ^{1}H NMR: ($CDCl_3$, 200 MHz): δ = 7−8.3 (m, 3H), 5.6 and 5.3 (s, 2H), 2.6 (q, 2H, J = 7.2), 1.2 (t, 3H, J = 8). IR (KBr): 3399 (alcoholic OH), 2856 (aromatic C−H), 1031 (C−O), 2925.6 (C−H, aliphatic).

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Notes

[†]Dr. Reddy's Communication No. IPDO IPM-IPDO IPM-00374.

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the management of Dr. Reddy's Laboratories Limited for giving support to carry out this work. We are also appreciative to the colleagues of analytical, PR&D, and process engineering departments for their cooperation, especially Dr. Amarendra Bhattacharya, Sandeep Reddy, and Alikepally Srinivasa Reddy, for helpful considerations.

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