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Scalable synthesis of 3-amino-2, 2-dimethylpropanamide: A key intermediate of Aliskiren

Sudhakar Reddy B.,[†]Srinivas Gangula,[*,†]Uday Kumar N.,[†] Naga Raju M.,[†]Panasa Reddy A.[‡]

[†]Integrated Product Development, Innovation Plaza, Dr.Reddy's Laboratories Ltd, Bachupally, Qutubullapur, R.R.Dist.700072, Andhra Pradesh, India; E-mail: sgangula@drreddys.com; Tel.: +91 4044346117; fax: +91 4044346285; [#]DRL-IPD Communication number: IPDO-IPM-00349

[‡]Department of Chemistry, Osmania University, Hyderabad.

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Abstract: A practical and scalable synthesis of 3-amino-2,2-dimethylpropanamide, a key intermediate of Aliskirenis described. Process optimization of dimethylation, ammonolysis and hydrogenation steps and their scale up challenges were discussed.

Keywords: Aliskiren, 3-amino-2, 2-dimethylpropanamide, Ammonolysis, Hydrogenation, Optimization

Introduction

Aliskiren (trade-names Tekturna, Rasilez) represents the first drug in the market being constituent of a novel class of rennin inhibitor developed by Novartis, with a huge potential for treatment of hypertension and related cardiovascular diseases.[1-2]Aliskirenchemically described as (2*S*,4S,5*S*, 7*S*)-5-amino-*N*-(3-amino-2,2-dimethyl-3-oxopropyl)-4-hydroxy-2-isopropyl-7-(4-methoxy-3-(3-methoxypropoxy)benzyl)-8-methylnonanamide (Fig 1).The 3-amino-2, 2-dimethylpropanamide intermediate is the essential fragment of Aliskiren.

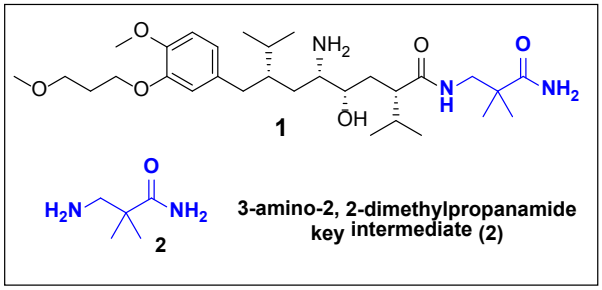
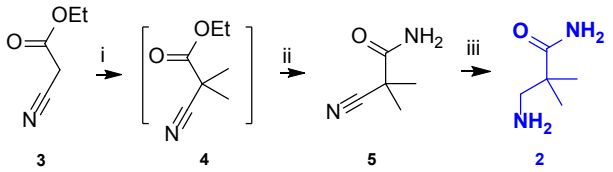


Fig1.Structure of Aliskiren (1) and 3-amino-2, 2-dimethylpropanamide

In our endeavor to support ongoing Aliskiren (**1**) project, we need to prepare multi kilogram quantities of key fragment **2**.There are number of reports on the synthesis of 3-Amino-2.2-dimethylpropanamide **2**.[3-7] However, in our approach we intended to develop analternative

multi kilogram scalable synthesis for compound **2**(Scheme 1).[8]

***Scheme 1*. Synthesis of 3-Amino-2.2-dimethylpropanamide* (2)**



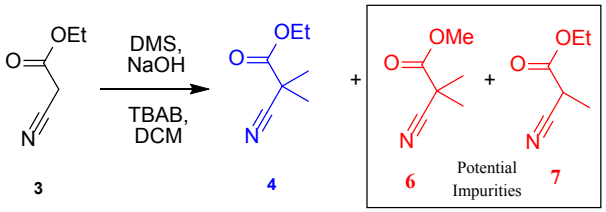
***Reaction condition**: i) DMS/NaOH /TBAB/DCM, Reflux, 4-6 h, ii) MeOH.NH_3 10-12 h, RT, iii) Raney Ni/NH_3/MeOH,10-12 h, H_2gas, 60-65°C

This synthesis involves three chemical transformations like Methylation, Ammonolysis and Hydrogenation. The route was extensively studied and optimized the process parameters subsequently addressed the various scale up issues.

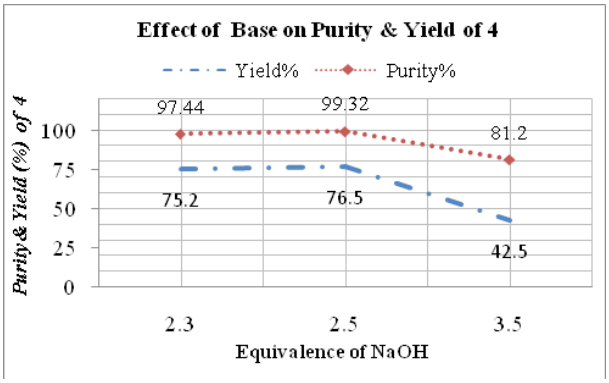
Results and Discussion:

Process Optimization of Methylation Step: The most critical step in the synthesis of **2** isdimethylationreaction, because the reaction generates the major amount of methyl ester**6** and monomethyl**7**impurities (scheme. 2), which subsequently affected the yield and purity of compound **4**. Hence, to minimize these impurities and improve the yields, we screened solvents (THF and DCM).Although the THF solvent able to give complete conversion, in view of the cost advantages, the DCM was opted as suitable reaction solvent. Further it was found the reaction is solvent dilution dependent, because lower the dilution of DCM (<10 vol) leads to incomplete reactions and lower yields. Hence in further experiments higher (~ 15 vol of DCM)reaction dilution was maintained during the course of reaction and minimized the impurities.

***Scheme 2*: Methylation Reaction**



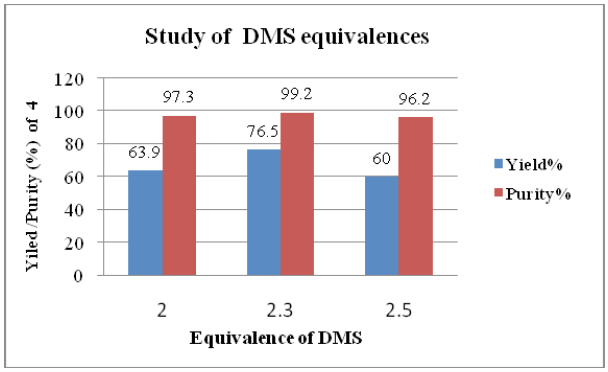
Most of the literature precedence approaches are utilized the sodium hydride (NaH) as base for dimethylation reaction. However use of unsafe sodium hydrideraises operational concerns for large scale production.In our approach we established the NaOH, Phase Transfer Catalyst (PTC) mediated dimethylation reaction and thus eliminated NaH from process. In this reaction the NaOH equivalentshas shown significant effect onrate of conversion and the isolated yields (Graph 1). It was noticed that, with 2 and 2.3 moles of NaOH reaction conditions did not went to completion. Further the higher equivalence of base (3.5eq) causes to hydrolysis of ester and that trigger to low yield. In subsequent study identified the 2.5 mole of base is the optimal condition for dimethylation reaction.



Graph1*: *Study of NaOH equivalence

After that we screened the equivalence of dimethyl sulphate (DMS) reagent. In this study it was observed that the stoichiometric amount of DMS (2 eq) conditions did not went to complete conversion and subsequently given only 64% yield. Indeed the 2.5 moles of DMS drives towards reaction completion it leads to impurities formation. As a result the isolated

yields were obtained only 60%. Up on close scrutiny of reaction with the 2.3 equivalence of DMS the yield was improved from 60 % to 76.5 % (graph 2).



Graph 2*: *Study of mole equivalences of DMS

Effect of Sequence and Mode of Addition: In the initialoptimization study, to the mixture of DCM,2-ethyl cyano acetate **3**, sodium hydroxide and tetra butyl ammonium bromide (TBAB) was slowly added the dimethyl sulphate at 0-5°C. In another mode of addition study charged the all raw materials and maintained the reaction. In these modes of additions, incomplete reaction and formation of number of impurities were observed. Hence further the addition sequence was changed to addition of mixture of DMS and 2-ethyl cyano acetate to the mixture of DCM, sodium hydroxide and TBAB at 0-15°C about 2-3h.Though in this sequence of addition obtained good yield, during the addition exothermic was noticed. Hence, prior to scale up we studied the reaction calorimetric (RC) and understand the enthalpy of reaction is -3907.77 KJ/kg; Δ Tad of 147.99 K. In view of these concerns, we examined the mode of DMS solution addition time and temperature. This study revealed that the fast addition of DMS solution lead to high exothermic and also observed the incomplete conversion of in-suit mono methyl (**7**) to dimethyl compound (**4**) (table 1, entry no 1). Further, though the longer addition (~6 h) of DMS solution is controlled reaction exotherm, ithas effect on esterhydrolysis and yield (entry 2). In subsequent optimization study identified the addition time as 3-4 h and temperature as 0-15°C (Table 1). In addition varying the reaction temperature to lower or higher directed to incomplete conversion of in-suit mono methyl (**7**) to dimethyl compound (**4**). Therefore, impetus was given to ensure the rate of addition was strictly controlled throughout the addition of DMS solution and efficient jacket cooling was given at scale up.

***Table 1:* Effect of DMS mixture solution addition time and temperature**

Entry	Addition Time(h)	Addition Temp(°C)	Yield (%)	Purity by GC (%)	
				4	7
1	0	0-5	78.9	96.38	1.17
2	5-6	0-5	68.5	95.52	0.99
3	3-4	-5-0	78.0	95.27	2.57
4	3-4	0-10	75.5	99.32	0.03
5	**3-4**	**0-15**	**74.6**	**98.38**	**0.09**
6	3-4	25-35	70.0	84.59	7.17

There after studied the reaction maintenance time, in this study after addition of DMS solution the reaction mass was heated to 35-40 °C and stirred for reaction completion. In this study varying the maintenance time and temperature effected the conversion and yield. Further maintain the reaction at 35-40°C for 4-6 hr given complete conversion with 76% yields (Table 2). Therefore the same reaction conditions were opted for further scale up batches.

***Table 2*: Study of Reaction Time and Temperature**

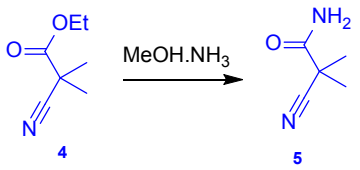
Entry	Time (h)	Temp (°C)	Yield (%)	Purity by GC (%)	
				4	7
1	2.5	35-40	77.1	95.8	0.99
2	**4-6**	**35-40**	**76.0**	**99.1**	**ND**
3	7-8	35-40	70.9	98.99	0.03
4	9-10	20-25	79.1	96.44	2.97

After completion of reaction it was quenched with water and separated DCM layer. Further the DCM layer was washed with water and

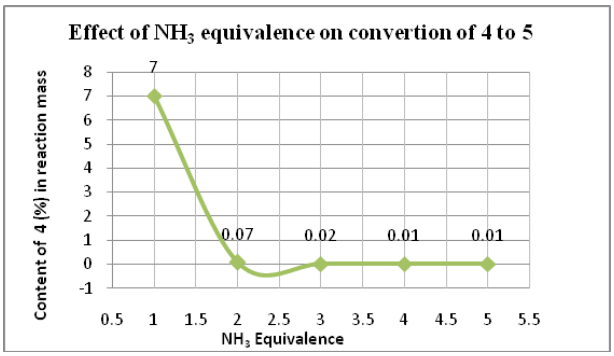
subjected for distillation.

Process Optimization of Ammonolysis of Ester: In order to achieve the ammonolysis reaction, we screened the different (1 to 5 eq) equivalence of NH_3(NH_3in Methanol)[9].

***Scheme 3*: Ammonolysis Reaction[11]:**

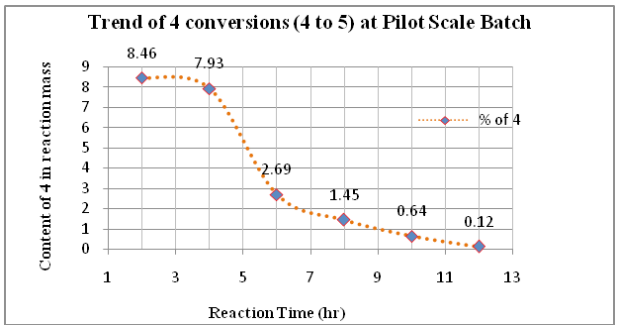


It was found that the reaction is NH_3equivalence dependent, because the reaction essentially required 2.5 or 3.0 equivalence for maximum conversion of **5**. With the stoichiometric mole of NH_3conditions un-reacted 7% of ester compound (**4**)(Graph 3) was observed. Further it was noticed that with the higher equivalence of NH_3lead to complete reaction with impurities. After the close investigation, identified the 3.0 equivalence of NH_3 is thesuitable quantity for ammonolysis reaction. During this study all the experiments was performed at 25-35 °C for 10-12 h.



Graph 3*: *StudyofNH$_3$equivalence(Lab Study)

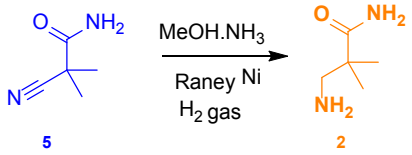
Further the optimized reaction conditions were tested at pilot scale (30 kg) and monitored the rate of conversion(**4** to **5**). The pilot scale batch results were clearly evidence that the performance of reaction was consistence with the laboratory observations (Graph4).



***Graph 4*:Trend of 4 conversions (4 to 5)at Pilot Scale Batch (30 kg)**

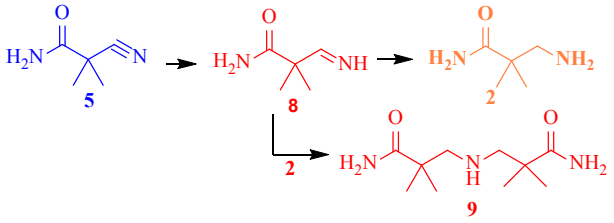
Investigation of Hydrogenation Step: After the solvent screen, methanol was selected as suitable system for hydrogenation reaction.

***Scheme 4:*Hydrogenation Reaction**



In this reduction step incomplete reaction and formation of major amount of symmetrical secondary amine impurity **9** was observed. It seems that during the reduction of **5**, addition of primary amine **2** to the intermediate imine species (**8**) is faster than hydrogen attack[10](scheme 5).

***Scheme 5*. Possible mechanism for symmetrical secondary amine impurity (9)**



However, close scrutiny of the reaction revealed that presence of Methanolic ammonia the conversion was improved and suppressed the formation of impurity **9**. Further the hydrogenation reaction was explored with Pd/C

and Raney Niand recognized that the reaction conversions was best with the Raney Ni catalyst system (Table 3).

***Table 3*: Selection of catalyst and its loading for hydrogenation of 5**

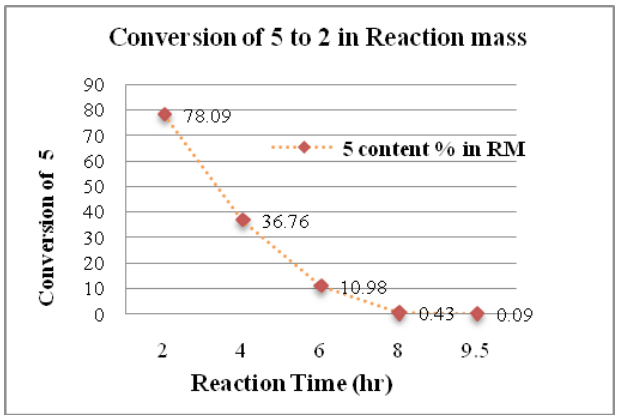
Entry	Catalyst	loading (w/w)	Purity by GC (%)	
			2	**5**
1	5% Pd/C	30	45.56	0.08
2	Raney Ni	15	89.80	4.35
3	**Raney Ni**	**20**	**99.42**	**ND**
4	Raney Ni	30	97.13	0.02

In this reduction, the catalyst loading have an effect on the conversion of **5**, because the lower load of (15%, w/w) catalyst cause to incomplete conversionand retain the 4.35% of compound **5**. Further it was observed with the higher (30% w/w) catalyst loading trigger to higher level impurities. Up on additional study the 20 % (w/w)of catalyst was found to be optimum quantity for hydrogenation reaction (Table 3).

***Table 4:* Reaction time and temperature for conversation of 5 to 2**

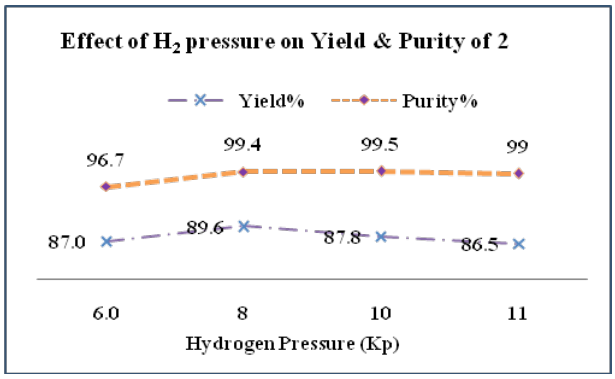
Entry	Time (hrs)	Temp (°C)	Purity by GC% **2**
1	10-12	55-60	92.03
2	10-12	65-70	96.56
3	**8-9**	**60-65**	**99.42**
4	14-16	60-65	98.83
5	10-12	60-65	99.52

There after we studied the reaction time and temperature for conversion of compound **2**. In this, lower the reaction temperature (< 55°C) leads to lower conversion and further longer the maintenance at this temperature failed to complete the reaction. In subsequent reaction investigation identified that maintain the reaction at 60-65°C for 8-9 hr is essential for the complete conversion of reaction. Further these optimal conditions were tested at pilot scale (15 kg) and monitored the reaction conversion. The pilot scale batch resultswere consistence with the laboratory observations and the maximum reaction conversion (0.09% of **5**) was within 8-9 hr (Graph 5).



***Graph 5:*Pilot Scale (15 Kg) Batch Reaction Mass Analysis (5 to 2)**

In consequent optimization study, we investigated the effect of hydrogen pressure on purity and yield of compound **2**. In this study acknowledged the 7-8Kp hydrogen pressure and 60-65°C temperature are the optimal conditions for hydrogenation reaction(Graph 6).



***Graph 6*: Effect of H_2pressure on Yield and Purity of 2**

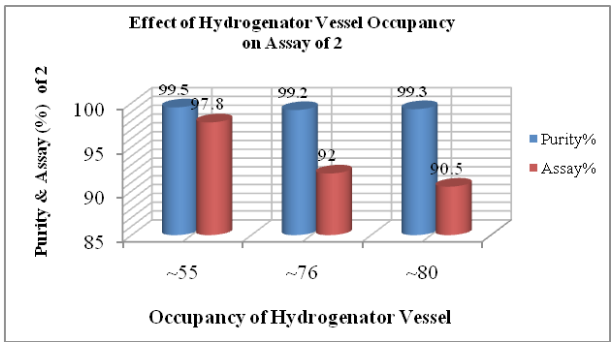
There after the optimized hydrogenation step was executed at pilot scale (3*15 kg batches) and quality results are summarized in table 5. Although the pilot scale batches weremeeting

the purity profile and those batches were failing in the assay specification of **2**(Assay Specification limit:Not Less Than: 97%).

***Table 5*: Pilot Scale Batches Quality Details (2)**[12]

Entry	Batch Size (kg)	Purity by GC (%)	Assay (%) (Limit: NLT: 97%)
1	15.0	99.07	89.95
2	15.0	97.28	84.94
3	15.0	98.27	85.08

To address the compound **2** assay issues, we re investigated the hydrogenation reaction with different conditions in small scale experiments. In this study we observed that the assay of compound **2** is depended on the occupancy of reaction mass in the hydrogenation vessel.



***Graph 7:*Effect of reaction mass occupancy on the assay and purity of 2**

Hence, much of the efforts were directed towards the study of different occupancies (such as 50%, 75% and 80%) of reaction mass. In this approach increasing the reaction mass occupancy decreasing the assay of compound **2** was noticed. While decreasing the occupancy of the mass increasing of assay was observed (Graph 7). The trend of assay results indicating that higher mass occupancy led to improper mass transfer of hydrogen gas and consumed higher hydrogen gas, subsequently that led to degradation of reaction and affected the assay of compound **2**. It was noticed that the above three pilot scale batches (3*15 kg) were executed in 200 L hydrogen vessel with 80% reaction mass occupancy. With this cause the reaction mass degraded and affected the assay ofpilot scale batches.

***Table 6:* Scale up batches details of 2**

Entry	Input (kg)	Occupancy %	Yield (%)	Purity by GC (%)	Assay (%)
1	10.0		85.8	99.52	**98.2**
2	10.0	~55	86.9	99.53	**98.7**
3	10.0		86.0	99.52	**98.4**

Therefore, further the lower reaction mass occupancy (~ 50-60 %) hydrogenation conditions were opted and proceeded to scale up study. In this pilot scale study the batch size was reduced from 15 kg to 10 kg and the batch was executedin 200 L hydrogenate vessel. In this pilot scale, all the three batches were meeting the purity and assay specification of compound **2**(Table 6).In this endeavor all the process variables and parameters were extensively investigated and provided the robust scalable process for compound **2** and prepared (120 kg of **2**) kilo gram quantities of **2**.

Recovery of Process Solvents: After completion of process intensification study for compound **2**, next we aimed to reduce the organic waste at production scale by recovering and reusing the process solvents such as ethyl acetate, dichloromethane of **2**. The process solvents (ethyl acetate, dichloromethane) were recovered by atmospheric distillation(Table 7).

***Table 7*: Recovered solvents details used for the reaction and isolation of 5**

Entry	Solvent	Purity by GC (%)
1	Fresh DCM	99.0
2	Recovered DCM	99.1
3	Fresh EtOAc	99.0
4	Recovered EtOAc	99.0

Further the recovered solvents were reused in the

preparation of compound **2**. The experimental results were consistent and comparable with the fresh solvents. Furthermore, the specifications of recovered ethyl acetate, dichloromethane were found to be similar to those of fresh solvent.

Conclusion: In conclusion, we have developed a robust multi kilogram scalable process for 3-Amino-2.2-dimethylpropanamide, a key intermediate of Aliskiren. The report also discussed the process optimization of dimethylation, ammonolysis and hydrogenation reactions and their scale up challenges.

Experimental Section

Materials and Instruments: All commercially available materials and solvents were used as received without any further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 70 MHz, respectively, on a Varian Gemini 200 MHz spectrometer. The chemical shift values were reported on δ scale in ppm with respect to TMS (δ 0.00 ppm) as internal standard. The ESI mass spectrum was recorded on 4000-Q-trap LC/MS spectrometer. FTIR spectrum was recorded on Perkin-Elmer model spectrum series FT-IR as KBr pellet.

Synthesis of ethyl 2-cyano-2-methylpropanoate (5): To a solution of dichloromethane (300 L, DCM), sodium hydroxide (26.74 kg, 663 mol), tetra butyl ammonium bromide (7.72 kg, 26.7mol) was slowly added the mixture of 2-ethyl cyano acetate (30 kg, 0.267mmol) and dimethyl sulphate (76.92 kg, 610mol) over period of 2-3 h at 0-25°C.After completion of additionthe reaction mass was heated to 35-40 °C and maintained for 5-6 h. Further the reaction mass was cooled to 0-5°C and quenched with water at below 10°C.After that the aqueous and organic layer was separated and the aqueous layer was extracted with DCM. After that, the combined DCM layers were washed with water and subjected for high vacuum distillation (HVD) at 140°C with 10 torr vacuum. Thus obtained in situ intermediate **4** (30kg, 212 mol) was dissolved in $MeOH.NH_3$ (108.37 kg, 637mol,10% assay) and stirred for 12-14 h at 25-35°C. After completion of reaction,it was distilled under vacuum and obtained crude compound **5**. Further the crude material was suspended in ethyl acetate (36 L) at 25-35 °Cand stirred for 2-3 h. Then the isolated solid was filtered and washed with ethyl acetate (15 L) and obtained **5** as a crystalline solid with 60 %yield.IR (KBr, cm^{-2}) 2228 (-CN), 1724 (C=O), 2800 ($-CH_3$),3550 ($C=ONH_2$). ^{1}H-NMR($CDCl_3$): δ 1.3 (6H,s), 5.6 (2H,s, *J*=4.7 Hz). ^{13}C NMR ($CDCl_3$): 164.9, 144.7, 140.2 and 140.

Preparation of 3-Amino-2.2-dimethyl propanamide (2): To a solution of **5** (10 kg, 79.2 mol) in methanol (12 L), was charged Raney Ni (2 kg, 20%) and $MeOH.NH_3$ (17.4 kg, 90.9 mol, assay 10%). Further the autoclave was closed and applied 7-8 $kg/cm^2$of hydrogen gas and heated to 60-65°C for 9-10 h. During the reaction the autoclave was pressurized with 7-8 kg/cm^2 H_2 gas at same temperature. After completion of reaction the catalyst was removed by filtration and the mother liquors were subjected for distillation at below 50 °C. Thus obtained crude was crystallized in ethyl acetate (10 L) and diisopropyl ether (20 L) at room temperature and obtained the compound **2** as a crystalline solid with yield 86% (8.90 kg).IR (KBr, cm^{-2}):3372 ($-NH_2$), 2968 (-CH), 1471.99,1408.05 and 1369.78(-CH), 1659 (C=O). ^{1}H-NMR($CDCl_3$): δ 1.16 (6H,s) 2.76 (2H, s),5.52 (1H, s), 7.27(1H, s).

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9. **Ammonia (NH_3) in Methanol**: Assay method (Titrimetry): Take a 250mL Iodine flask and transferred 35 mL of 1N H_2SO_4 solution (nearly 7.35mL of conc. H_2SO_4 in 250mL water) into the iodine flask and add small amount of ice cubes, then close the flask with the lid and take the tare weight. Transfer 2mL of the test sample into the Iodine flask and take the weight, to this add methyl red as indicator. The resulting pink color solution is titrated against with 1N NaOH solution (10g in 250 mL).The end point is pink to pale yellow.
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11. **G.C method for 5 Analysis:** Compound **5** puritywas determined by gas chromatography.[Column DB-624 or equivalent, 30 Mts × 0.32 mm i.d., 1.8 μm film thickness,injection volume: 1.0 μL, injector temperature 180 °C, and detector temperature 260° C, injection mode/ ratio: split/1.5. Carrier gas flow used 2.0 psi (Helium)]. Column initially held at 70 °C for 5 min, then rise to 250 °C at a rate of 20 °C per 1 min and held at 250° C for 30 min.
12. **G.C method for 2:** Compound **2** puritywas determinedby gas chromatography.[Column DB-624 or equivalent, 30 Mts × 0.32 mm i.d., 1.8 μm film thickness, injection volume: 1.0 μL, injector temperature 140 °C, and detector temperature 260° C (FID), injection mode/ratio: split/1.5]. Carrier gas flow used 15.0 psi (Helium). Column initially held at 70 °C for 5 min, then rise to 250 °C at a rate of 20 °C per 1 min and held at 250° C for 30 min.