Chapter 2

A facile route to synthesis of 3-quinuclidinone hydrochloride

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An Improved and Simple Route for the Synthesis of 3-Quinuclidinone Hydrochloride

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Abstract: An improved method for the synthesis of 3-quinuclidinone hydrochloride **4** from piperidine-4-carboxylic acid **1** has been described. Reaction of piperidine-4-carboxylic acid **1** with thionyl chloride and ethanol gave ethyl piperidine 4-carboxylate **2**. It was further condensed with methyl chloroacetate in presence of sodium carbonate to give ethyl 1-(2-methoxy-2-oxoethyl)piperidine-4-carboxylate **3**. One pot Dieckmann reaction of **3** in presence of potassium *tert*-butoxide followed by hydrolysis and decarboxylation gave title compound azabicyclo[2.2.2]oct-3-one hydrochloride **4**.

Keywords: 3-quinuclidinone hydrochloride, Dieckmann reaction, isonepecotic acid, Gram scale synthesis.

INTRODUCTION

The quinuclidine is ring system found in a number of natural products [1]. It is also used in preparation of various therapeutically important molecules and also important intermediate and synthesis of some drugs like azasetron, benzoclidine, palonosetron, solifenacin, cevimeline, quinupramine etc [2]. Various quinuclidinone derivatives have been reported to show various biological activities [3-6]. Quinuclidinone derivatives are reported to show anti-cancer [7-8], anti-inflammatory [9], central nervous system stimulating activity [10] and antihistaminic activity [11]. Quinuclidinone has been also used in synthesis of some catalysts which are useful in asymmetric reactions such as aldol reaction [12-14]. Henry and aza Henry reaction [15] and Diels-Alder reaction [16]. Synthesis of quinuclidinone hydrochloride [17] involves multistep organic synthesis. So, we thought of designing relatively simple and safer route for the synthesis of 3-quinuclidinone hydrochloride.

The most useful approach for the construction of quinuclidinone ring is Dieckmann cyclization [18]. Literatures reveal a method for the synthesis of quinuclidinone hydrochloride [17] which has various disadvantages. The main disadvantage is pyridine ring which has serious health concerns. Secondly, it involves a high pressure reaction at a high temperature using very expensive catalyst like Pd/carbon. These disadvantages make this method unsuitable for large scale production. The present method utilizes isonepecotic acid as the starting material so that the hydrogenation step can be avoided. Herewith, we report relatively shorter and safer route which does not involve any harsh conditions, chromatographic purifications or expensive catalyst. Thus this method is cost-effective and easy to scale up.

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RESULT AND DISCUSSION

Esterification of isonipecotic acid **1** in presence of thionyl chloride and ethanol gave ethyl piperidine 4-carboxylate **2** as shown in Scheme **1**. In FTIR, band at 1734 cm^{-1} indicated presence of ester group. In ^1H NMR triplet at δ 1.02 for three protons and quartet at δ 3.88 for two protons indicated presence of ethyl group thus confirming formation of **2**. Further condensation of 2 with mono methyl chloroacetate in presence of base like sodium carbonate gave ethyl 1-(2-methoxy-2-oxoethyl) piperidine-4-carboxylate **3**. In FTIR, band at 1739 cm^{-1} indicated presence of ester group. In ^1H NMR triplet at δ 1.04 and quartet at δ 3.88 for ethyl and singlet at δ 3.51 for methyl thus confirmed formation of **3**. We have tried various reagents and solvents for Dieckmann condensation of ethyl 1-(2-methoxy-2-oxoethyl) piperidine-4-carboxylate **3** to convert it in to ethyl 3-oxoquinuclidine-2-carboxylate as shown in Table **1**. Potassium *tert*-butoxide gave better conversion to ethyl 3-oxoquinuclidine-2-carboxylate compared to sodium methoxide and potassium methoxide but it was very difficult to isolate.

We have also tried to optimize conditions with various acids for hydrolysis and decarboxylation to get azabicyclo[2.2.2]oct-3-one **4** as shown in Table **2**. Optimum result was obtained with HCl while in the case of H_2SO_4 and H_3PO_4 the yield was below 50%. The product was further converted into its hydrochloride salt by purging HCl gas. In FTIR, band at 1748 cm^{-1} indicated presence of carbonyl of which confirmed formation of **4**.

EXPERIMENTAL DETAILS

Reagent grade chemicals and solvents were purchased from commercial supplier and used without purification. TLC was performed on silica gel F254 plates (Merck). Melting points are uncorrected and were measured in open capillary tubes, using a Rolex melting point apparatus. IR spectra were recorded as KBr pellets on Perkin Elmer RX 1 spec-

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2.1 Introduction

The quinuclidine ring system found in a number of natural products.[1] It is also used in synthesis of various therapeutically important molecules and intermediate of some drugs like azasetron, benzoclidine, palonosetron, solifenacin, cevimeline, quinupramine etc.[2] Various quinuclidinone derivatives have been reported to show various biological activities.[3,4,5,6] Quinuclidinone derivatives are reported to show anti-cancer,[7,8] anti-inflammatory,[9] central nervous system stimulating activity[10] and antihistaminic activity.[11] Quinuclidinone has been also used in synthesis of some catalysts which are useful in asymmetric reactions such as aldol reaction,[12,13,14] Henry reaction, Aza Henry reaction[15] and Diels-Alder reaction.[16] Synthesis of quinuclidinone hydrochloride[17] involves multistep organic synthesis. So, we thought to design relatively simple and safer route for the synthesis of 3-quinuclidinone hydrochloride.

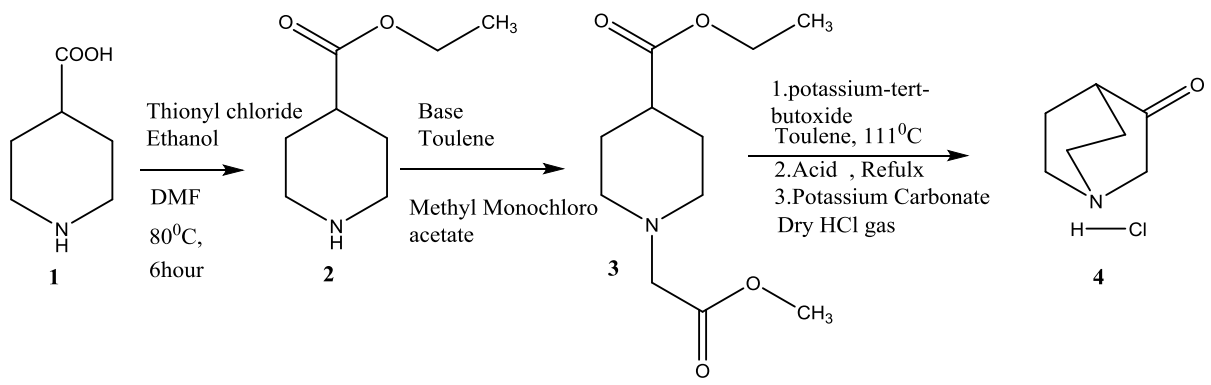
The most useful approach for the construction of quinuclidinone ring is Dieckmann cyclization.[18] Literature reveals only one method for the synthesis of quinuclidinone hydrochloride[17] is reported which has various disadvantages. The main disadvantage is pyridine ring which has many serious health concerns. Secondly, it involves a high pressure reaction at a high temperature using very expensive catalyst like Pd/carbon. These disadvantages make this method unsuitable for large scale production. The present method utilizes isonipecotic acid as the starting material so that the hydrogenation step can be avoided. Herewith, we are reporting relatively shorter and safer route which does not involve any harsh conditions, chromatographic purifications or expensive catalyst, thus this method is cost-effective and easy to scale up.

2.2 Result and Discussion

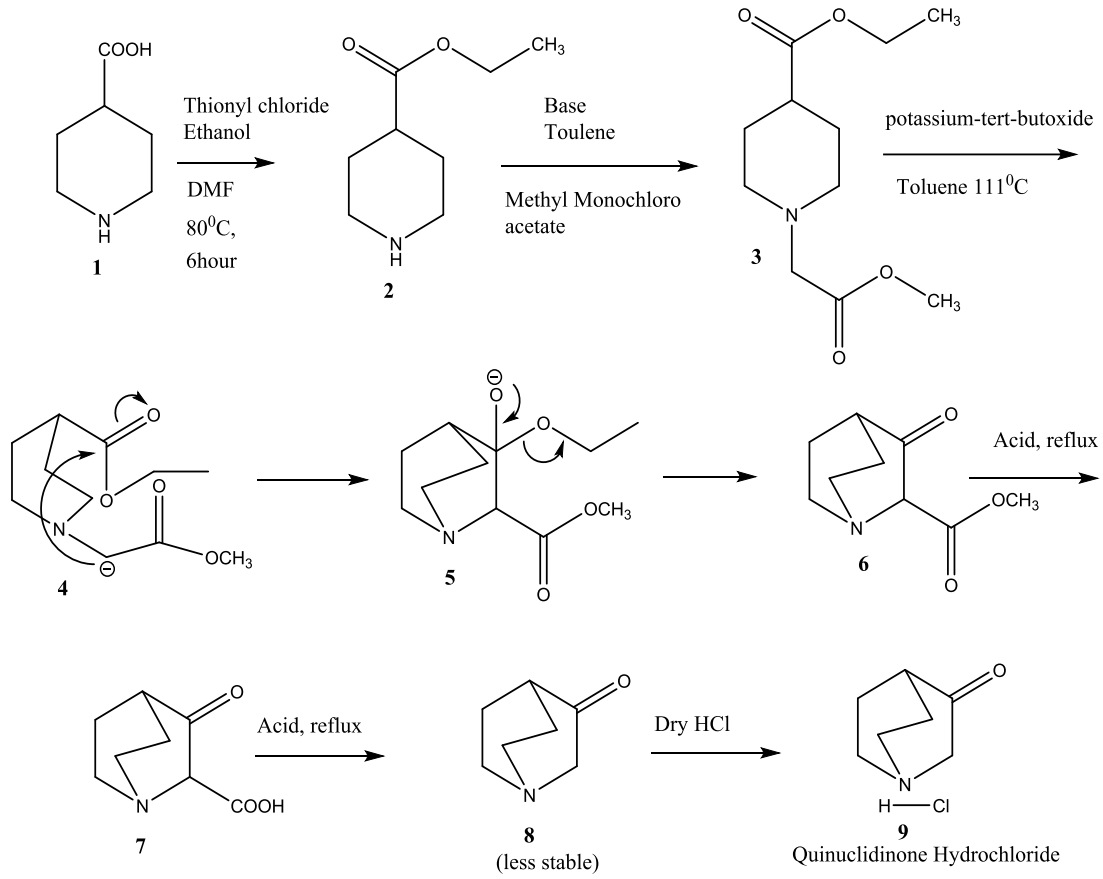
Esterification of isonipecotic acid **1** in presence of thionyl chloride and ethanol gave ethyl piperidine 4-carboxylate **2** as shown in Scheme 1. In FTIR, band at 1734 cm^{-1} indicated presence of ester group. In ^1H NMR triplet at δ 1.02 for three protons and quartet at δ 3.88 for two protons indicated presence of ethyl group thus confirming formation of **2**.

Further condensation of **2** with mono methyl chloroacetate in presence of base like sodium carbonate gave ethyl 1-(2-methoxy-2-oxoethyl)piperidine-4-carboxylate **3**. In IR, band at 1739 cm^{-1} indicated presence of ester group. In ^1H NMR two triplets at δ 1.04 and 3.51 for three protons each, two quartets at δ 2.69 and 3.88 for two protons were obtained which indicated presence of two ethyl group and one singlet at δ 3.03 for two protons thus confirmed formation of **3**.

We have tried various reagents and solvents for Dieckmann condensation of ethyl 1-(2-methoxy-2-oxoethyl)piperidine-4-carboxylate **3** to convert it in to ethyl 3-oxoquinuclidine-2-carboxylate as shown in Table 2.1. Potassium tert-butoxide gave better conversion to ethyl 3-oxoquinuclidine-2-carboxylate compared to sodium methoxide and potassium methoxide but it was very difficult to isolate. We have also tried various acids for hydrolysis followed by decarboxylation to get Azabicyclo[2.2.2] oct-3-one **4** and further converted it in to its HCl salt by purging HCl gas. We attempted the optimization of decarboxylation step by using different acid as shown in Table 2. Optimum result was obtained with HCl while in the case of H_2SO_4 and H_3PO_4 yield was less than 50%. In IR, band at 1748 cm^{-1} indicated the presence of carbonyl which confirms formation of **4.**



Scheme 1: Synthetic scheme for the synthesis of Quinuclidinone Hydrochloride



Scheme 2: Probable mechanism of Dieckmann condensation

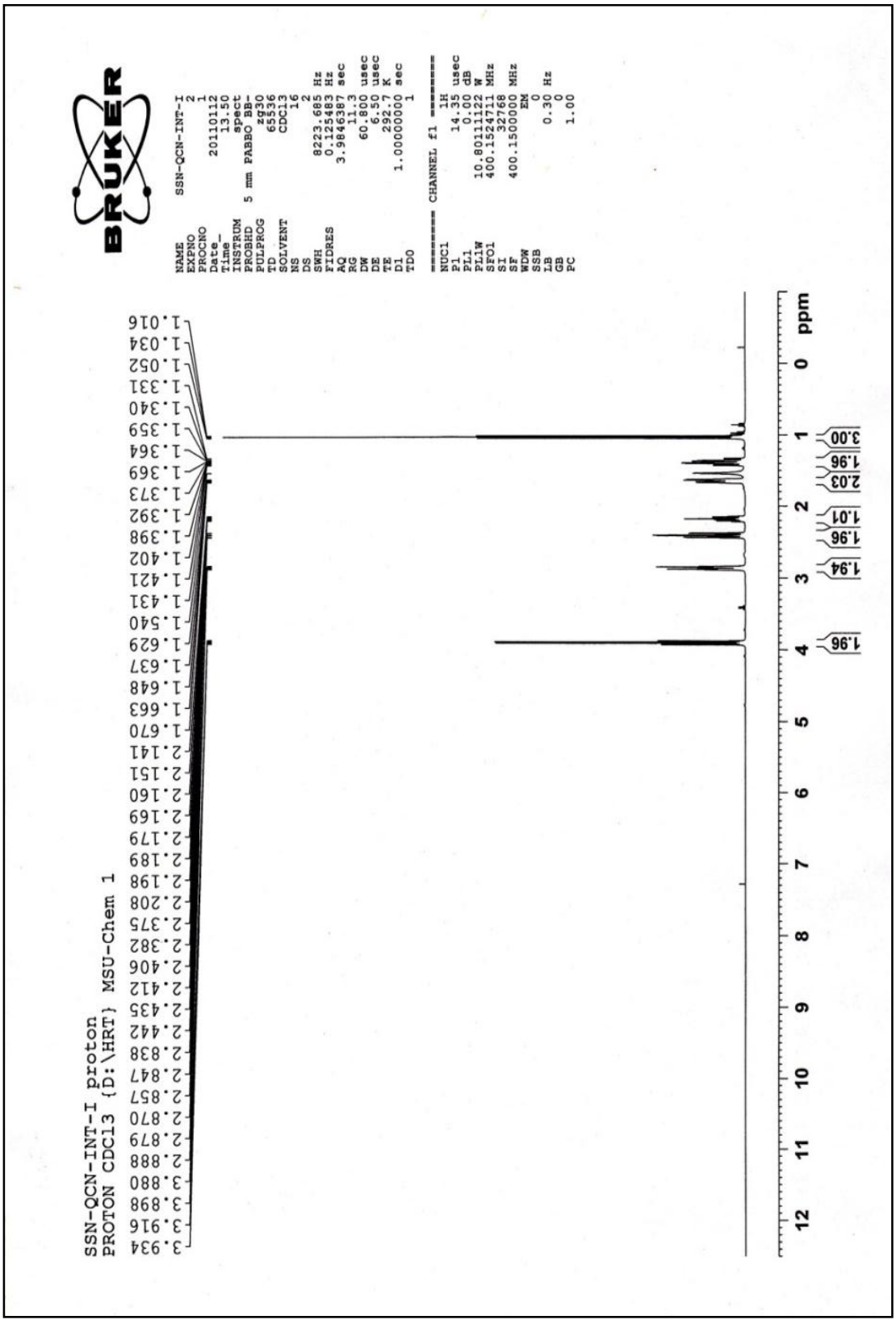


Figure 1: ^{1}H NMR of Ethyl piperidine 4-carboxylate 2

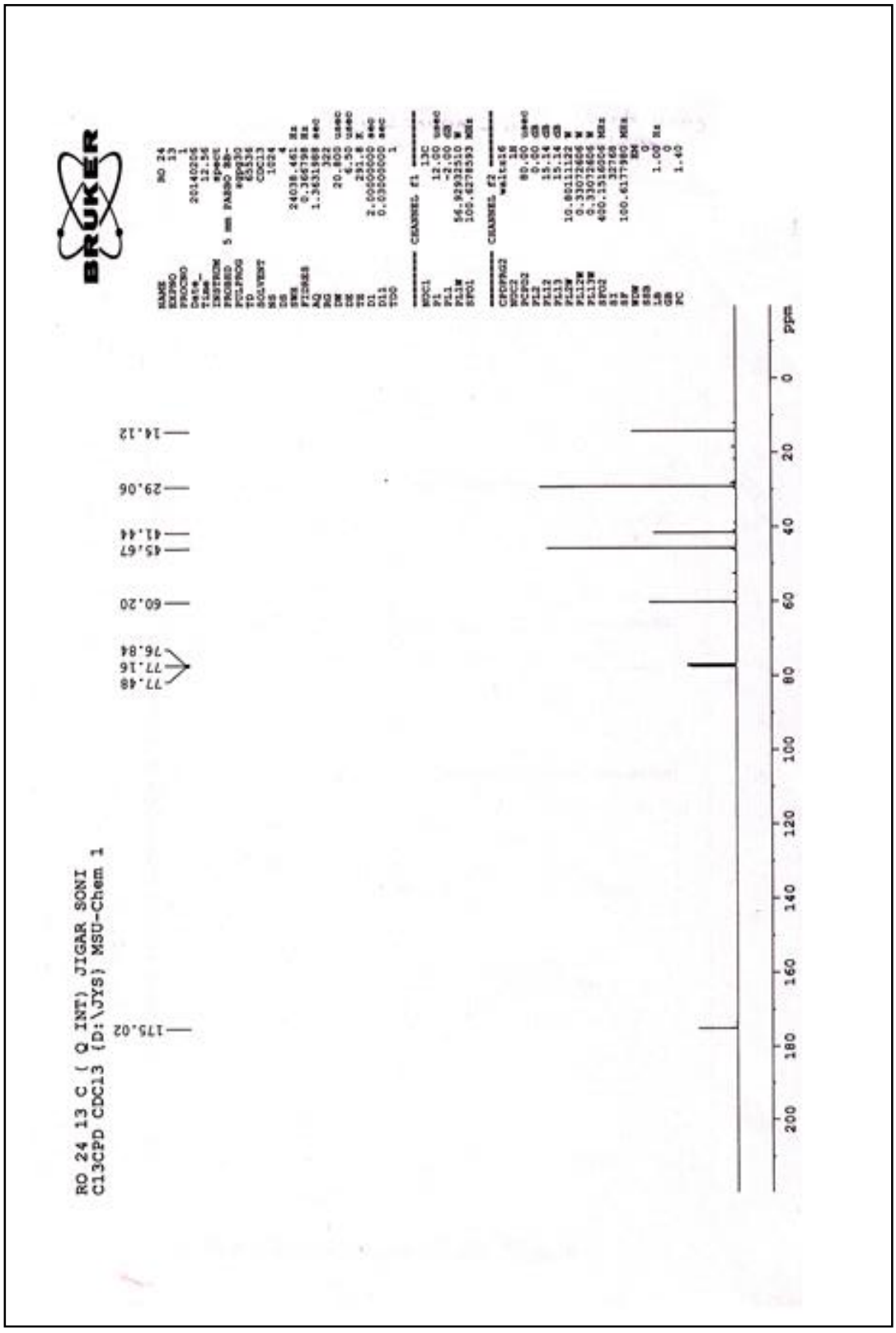


Figure 2: ^{13}C NMR of Ethylpiperidine 4-carboxylate 2

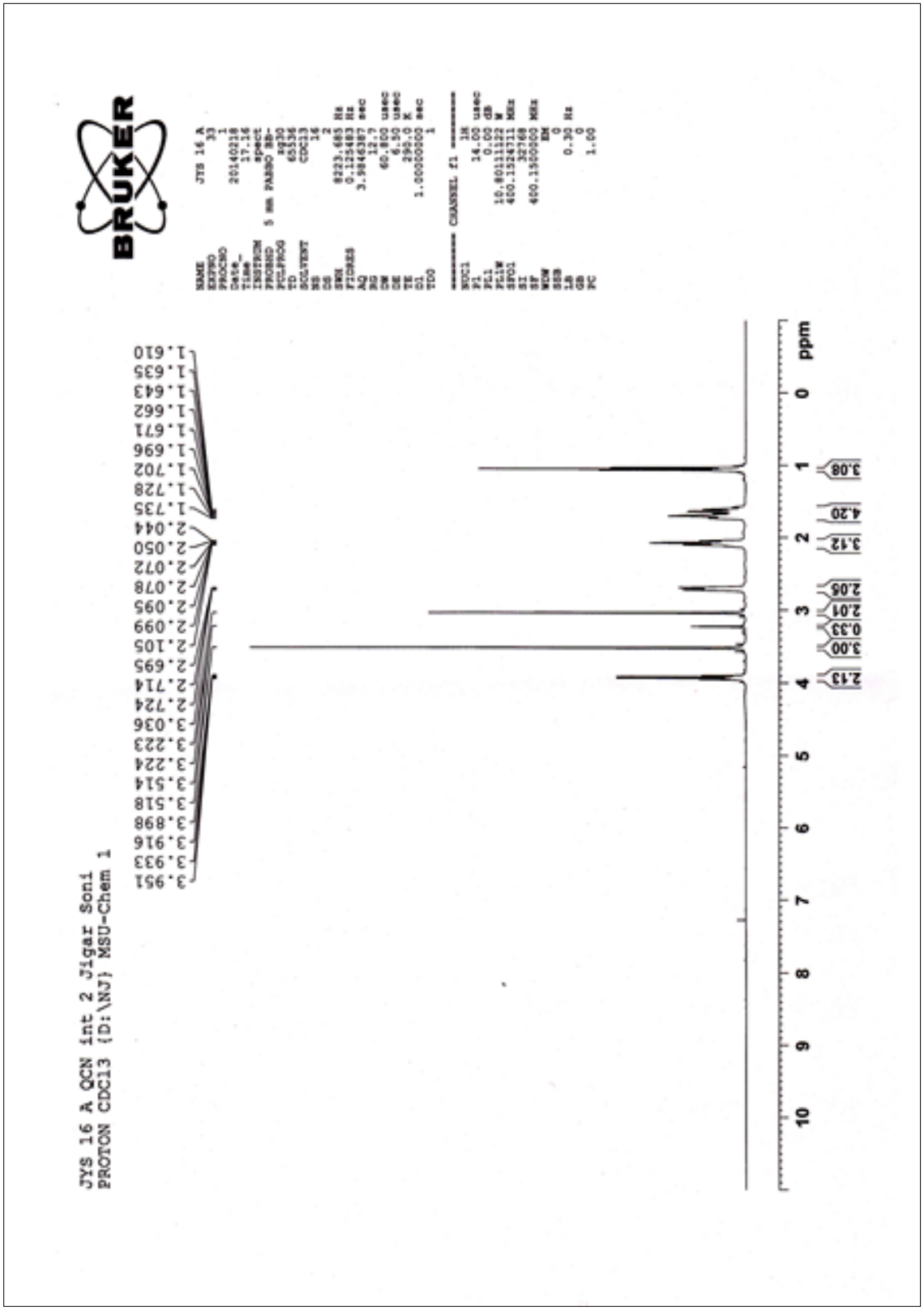


Figure 3: ^{1}H NMR of Ethyl 1-(2-methoxy-2-oxoethyl)piperidine-4-carboxylate 3

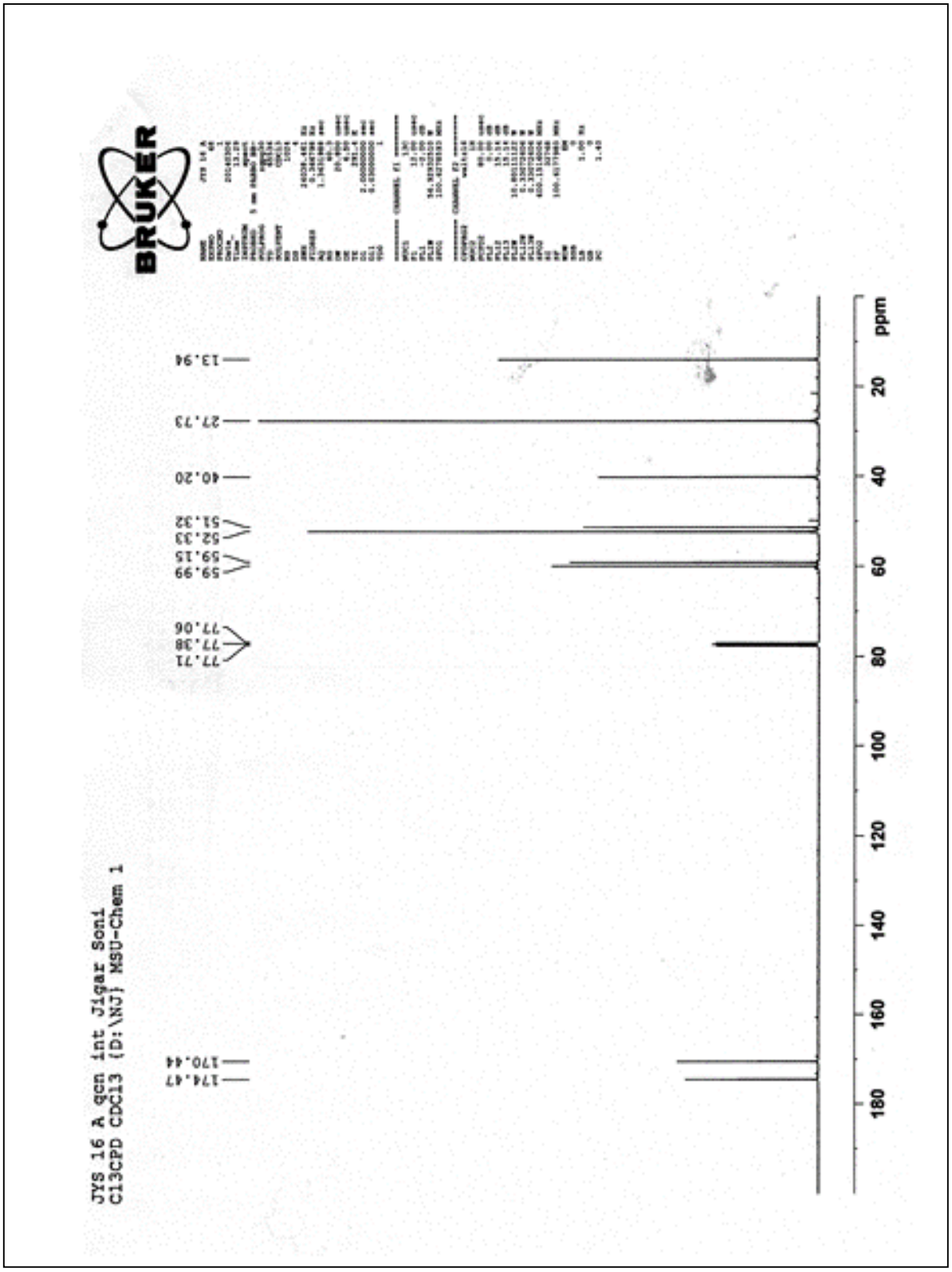


Figure 4: ^{13}C NMR of Ethyl 1-(2-methoxy-2-oxoethyl)piperidine-4-carboxylate 3

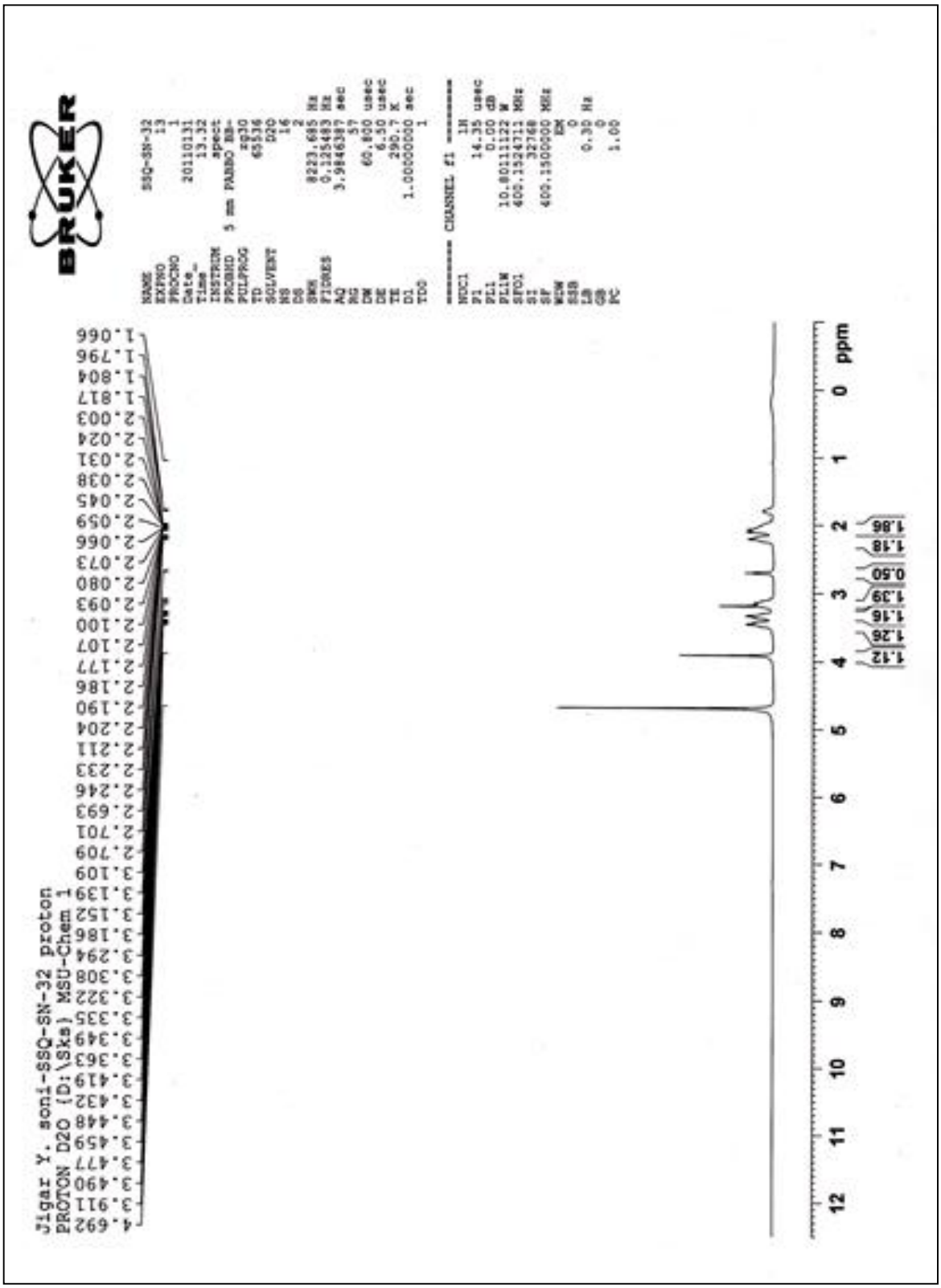


Figure 5: ^{1}H NMR of quinuclidinone hydrochloride 4

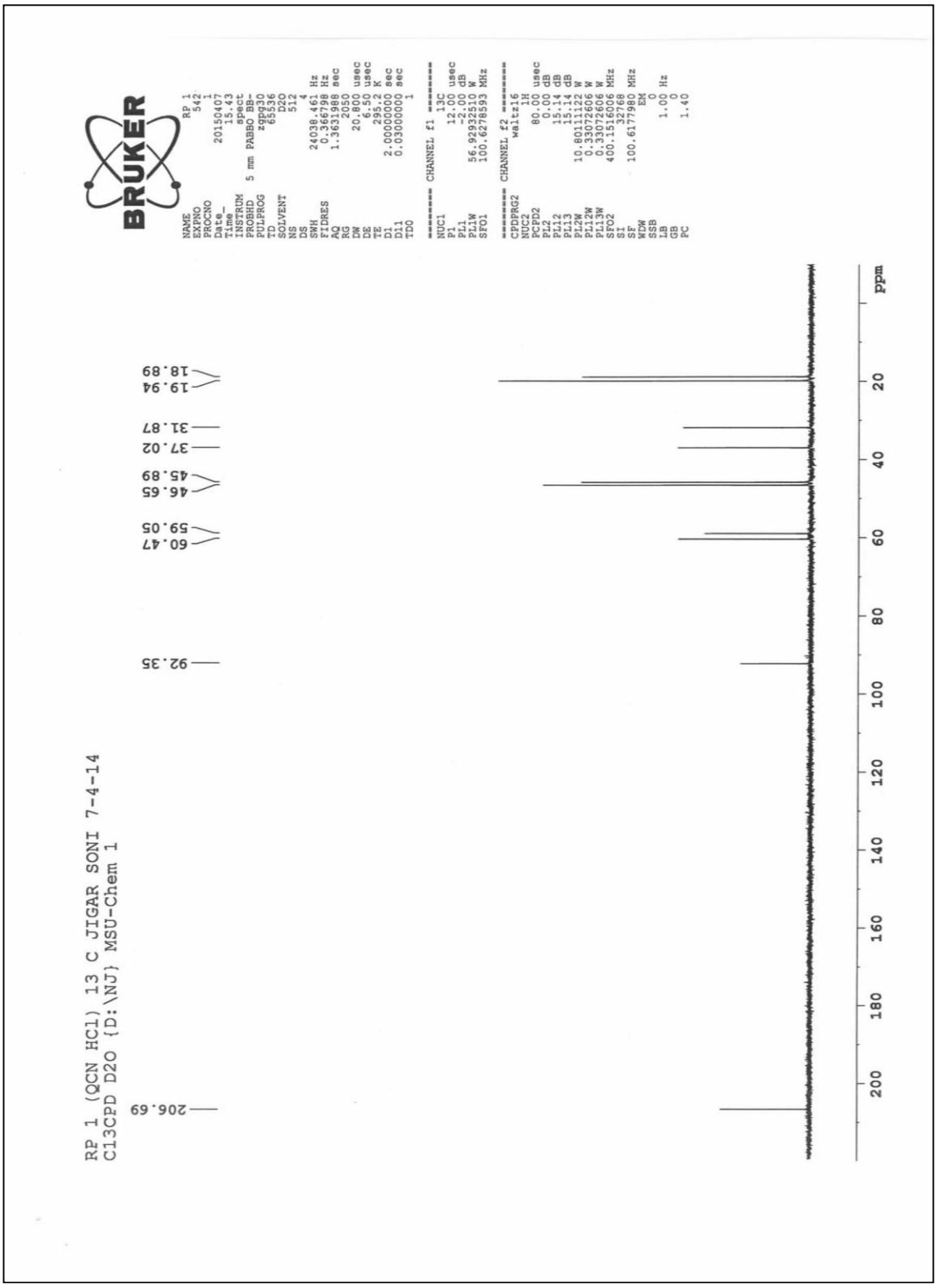


Figure 6: ^{13}C NMR of quinuclidinone hydrochloride 4

We also made attempts to use different bases in different solvents for the cyclisation step **Table 2.1**. Reaction did not progress when sodium methoxide was used at different concentrations (Entry no: **1**, **2**, **3**). In addition to that commercially available sodium methoxide or freshly prepared sodium methoxide (Entry no: **4**, **5**) both failed to the give product. Fruitful results were obtained when potassium metal was used for the cyclisation step. *In situ* generation of potassium ethoxide gave excellent result (Entry no: **7**). Commercially available potassium-tert-butoxide also gives good yield (Entry no: **8**). Slight decrease in the yield can be attributed to the small amount of impurities probably present in potassium-tert-butoxide. Replacing toluene with other solvent such as xylene or benzene did not have any significant effect on the yield of quinuclidinone hydrochloride.

Table 2.1 Reaction condition optimization for the *in situ* cyclisation reaction of quinuclidinone hydrochloride

S. No.	Reagent (mole)	Solvent	% isolated yield
1	Na\Methanol (0.068\0.068)	Toluene	No reaction
2	Na\ Methanol (0.055\0.055)	Xylene	,,
3	Na\ methanol (0.072\0.072)	Xylene	,,
4	28% NaOMe in methanol (0.078)	Methanol	,,
5	28% NaOMe (0.073)	Toluene	,,
6	Potassium-tert-butoxide (0.163)	Toluene	65
7	K\Ethanol (0.163\0.163)	Toluene	80

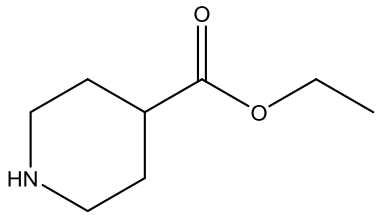
Reaction conditions: ethyl1-(2-methoxy-2-oxoethyl) piperidine-4-carboxylate (**3**), mole concentration: 0.065 mole and reaction time 16h.

Table 2.2 Reaction condition optimization for the *in situ* decarboxylation reaction of quinuclidinone hydrochloride

Entry	Acid	Isolated yield (%)
1	20% H_2SO_4	22
2	15% H_2SO_4	44
3	20%H_3PO_4	37
4	17% H_3PO_4	39
5	15% H_3PO_4	39
6	10N HCl	60
7	6N HCl	80
8	4N HCl	77

Reaction conditions: ethyl1-(2-methoxy-2-oxoethyl)piperidine-4-carboxylate **3** (0.065 mol), potassium metal (0.16 mol), absolute ethanol (0.17 mol), toluene (200 mL). Cyclization reaction gave acid intermediate 7, which is subjected to decarboxylation for generation of desired product. Various concentrations of acid used for the *in situ* decarboxylation (**Table 2.2**). When sulphuric acid is used product formation is seen in the range of 22% to 44%. Ortho-phosphoric acid gives moderate yield (entry 1-5). Hydrochloric acid gives yield in good amount. Reaction condition was optimized when 6N HCl was used for decarboxylation.

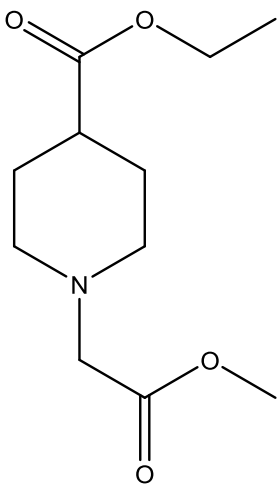
2.3 Experimental Details.



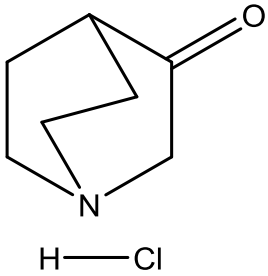
Ethyl piperidine 4-carboxylate2[19]: To a solution of isonipecotic acid **1** (50.0 g, 0.38 mol) in methanol (0.5 L), thionyl chloride (37.1 g, 0.50 mol) was added

dropwise in nitrogen atmosphere at 0 °C. After addition, reaction was heated to reflux temperature under nitrogen atmosphere for 6 h. Excess methanol was distilled out to give yellow paste which was dissolved in ethyl acetate (1 L) and neutralized with saturated sodium bicarbonate solution. Organic layer was dried by using sodium sulphate and concentrated to afford **2** (56.0 g, 92%) as colorless liquid.IR (neat) cm^{-1}: 3296, 2949, 2856, 2812, 2739, 1734; ^{1}H NMR ($CDCl_3$, 400 MHz) (Figure 1): δ 1.04 (3H, t, *J*=7.2 Hz, CH_3), 1.33-1.43 (2H, m, CH_2), 1.65 (2H, dd, CH_2), 2.14-2.21 (1H, m, CH), 2.37-2.44 (2H, m, CH_2), 2.83-2.87 (2H, m, CH_2), 3.90 (2H, q, *J*=7 Hz, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) (Figure 2): δ 14.1, 29.0, 41.4, 45.6, 60.2, 175.0.

Ethyl 1-(2-methoxy-2-oxoethyl) piperidine-4-carboxylate 3: To a solution of ethyl



piperidine 4-carboxylate**2** (50.0 g, 0.31 mol) in dry toluene (1.5 L), sodium carbonate (33.7 g, 0.31 mol.) was added. Methyl-2-chloroacetate (36.2 g, 0.33 mol.) was added dropwise at a rate so as to maintain the reaction temperature 45 °C. The reaction mixture was stirred for 4 h at rt. After the completion, the reaction mixture was washed with water till neutral pH. Organic layer was dried and toluene was distilled out under vacuum at 70 °C to afford **3** as yellow liquid (55.4 g, 76%). IR (neat) cm^{-1}: 2951, 2812, 2775, 1739, 1029. ^{1}H NMR ($CDCl_3$, 400 MHz) (Figure 3): δ 1.05 (3H, t, *J*=7 Hz, $-CH_3$), 1.57-1.73 (4H, m, $-2CH_2$), 2.04-2.10 (3H, m , $-CH_2$, -CH), 2.69-2.72 (2H, m, $-CH_2$), 3.03 (2H, s, $-NCH_2O$), 3.52 (3H, s, $-0CH_3$), 3.90 (2H, q, *J*=7 Hz, $-CH_2$).^{13}C NMR ($CDCl_3$, 100 MHz) (Figure 4): δ 13.9, 27.7, 40.2, 51.3, 52.3, 59.1, 59.9, 170.4, 174.5



Azabicyclo[2.2.2]oct-3-one hydrochloride 4[17]: In dry toluene (1.0 L) potassium-*tert*-butoxide (30.62 g, 0.27 mol) was added under nitrogen atmosphere. Next, the reaction mixture was refluxed for 30 min under nitrogen atmosphere. Ethyl 1-(2-methoxy-2-oxoethyl)piperidine-4-carboxylate **3** (25.0 g, 0.21 mol) in 1.0 L dry toluene was added to the reaction mixture dropwise so that addition will complete in 3 h at reflux condition under nitrogen atmosphere. Progress of reaction was monitored by TLC. After completion, the reaction mixture was cooled to 0-5 $^{\circ}$C and cold 6 N HCl (1.0 L) was added. The aqueous layer was separated and refluxed for 14 h for hydrolysis and successive decarboxylation. Reaction mass was neutralized by adding saturated K_2CO_3 solution and product was extracted in ethyl acetate (1.0 L). Organic layer was acidify by purging dry HCl gas and was evaporated to afford **4** as colorless solid (14.0 g, 80%).Mp 300 $^{\circ}$C.[17], IR: (neat) cm^{-1}: 2965, 2907, 2764, 1748; ^{1}H NMR (D_2O, 400 MHz) (Figure 5): δ 1.79-1.81 (0.5H, m), 2.00-2.10 (1.5H, m), 2.17-2.24 (1H, m), 2.69-2.70 (0.5H, t), 3.10-3.18 (1H, m), 3.29-3.36 (1H, m), 3.41-3.49 (1H, m), 3.91 (1H, s). ^{13}C NMR (D_2O, 100 MHz) (Figure 6): δ 18.8, 19.9, 31.8, 37.0, 45.8, 46.6, 59.0, 60.4, 92.3, 206.6.

2.4 Conclusion

An efficient three step method for the synthesis of 3-quinuclidinone hydrochloride has been developed. The present method utilizes isonepecotic acid as the starting material which omits hydrogenation step and use of expensive catalyst. This method has advantage of being cost effective, facile and safe for the synthesis of 3-quinuclidinone hydrochloride.

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