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REGULAR ARTICLE

Reinvestigating the synthesis of key intermediates in the preparation of zolazepam—I: (5-chloro-1,3-dimethyl-1H-pyrazol-4-yl) (2-fluorophenyl) methanone

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Abstract. The synthesis of (5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)(2-fluorophenyl) methanone (**IV**) as the key intermediate in the preparation of zolazepam is reconsidered. The previous report for the preparation of this compound consist of acylation of 5-chloro-1,3-dimethylpyrazole (prepared from chlorination of 1,3-dimethyl-5-pyrazolone) by 2-fluorobenzoyl chloride (**II**). Herein, the preparation of (**IV**) *via* chlorination of (5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)(2-fluorophenyl) methanone (**III**) which was prepared by acylation of 1,3-dimethyl-5-pyrazolone (**I**) by **II** is investigated. Different aspects of each step (reaction conditions, side products and workup procedure) were considered and the products and side products were characterized *via* ^{1}H NMR, ^{13}C NMR and GC-MS techniques.

Keywords. Zolazepam; 1,3-dimethyl-5-pyrazolone; (5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)(2-fluorophenyl) methanone; (5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)(2-fluorophenyl) methanone; 1,3-dimethylchromeno[2,3-c]pyrazol-4(1H)-one.

1. Introduction

A mixture of zolazepam and tiletamine (sold out under the name Telazol) is used as a tranquilizer for wild animals, such as gorillas and polar bears. In the only reported method for the synthesis of zolazepam (by Dewald *et al.* in the Parke-Davis institute), 5-chloro-1,3-dimethyl-1H-pyrazol-4-yl) (2-fluorophenyl) methanone (**IV**) is used as the key starting compound. The overall procedure for pyrazolodiazepinone synthesis such as zolazepam was synthesized *via* methyl amination of **IV**, acylation of the produced amino ketone by bromoacetyl bromide, conversion of bromoacetamide derivative to the azidoacetamide, catalytic hydrogenation of the azidoacetamide derivative and cyclization to the diazepinones (Scheme 1).[1,2]

The synthesis of **IV** has been reported (with a yield of 82%) by the Friedel-Crafts reaction between 2-fluorobenzoyl chloride and 5-chloro-1,3-dimethylpyrazole which has been suggested to be prepared by chlorination of 1,3-dimethyl-5-pyrazolone (**I**), itself synthesized by the reaction of methyl esters of alkylacetylenecarboxylic acids with methylhydrazines (Scheme 2).[3]

Some consideration should be made concerning this procedure. Firstly, the Friedel-Crafts reaction is expected to fail because the aroyl chloride is susceptible to the action of aluminum chloride and self-arylation. In the other part, 5-chloro-1,3-dimethylpyrazole is supposed to be synthesized by the reaction of 1,3-dimethyl-5-pyrazolone and $POCl_3$[2] without mentioning the yield. In fact, this reaction is reported for different 1,3-dialkyl-5-pyrazolone else 1,3-dimethyl derivatives.

We have studied this reaction under the same conditions that have been previously reported ($POCl_3$, reflux, 24 h)[2] without obtaining the targeted product. We have previously reported the conditions following which solvent-less reaction of ethyl acetoacetate with methyl hydrazine afford the quantitative amount of

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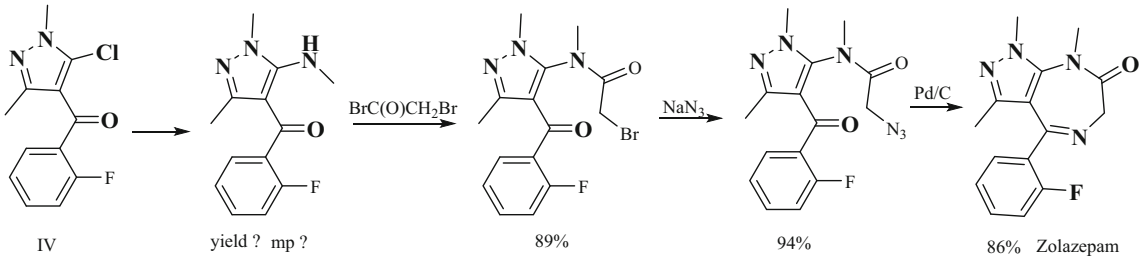
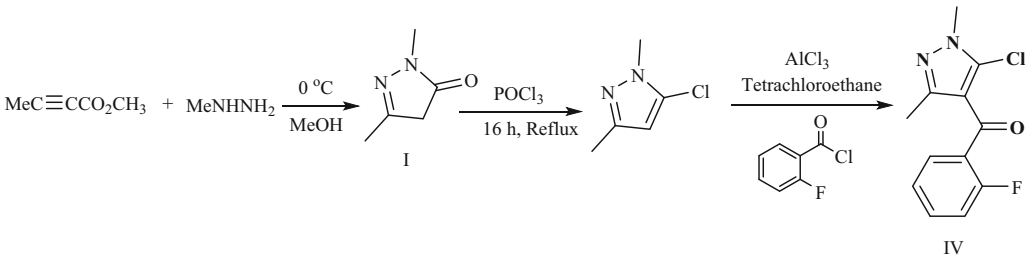


Scheme 1. Zolazepam synthesis *via* **IV** as intermediate[1,2].



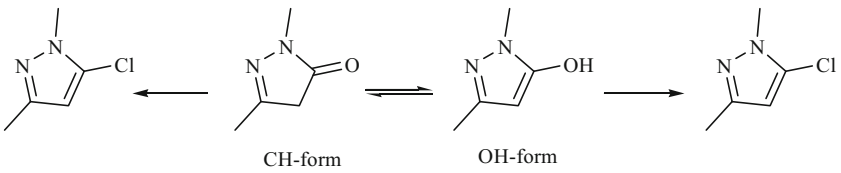
Scheme 2. Synthesis of **IV** *via* 5-chloro-1,3-dimethylpyrazole[3].

I (R ~ 100%), and investigated the tautomeric forms of **I** by ^{13}C and ^{1}H NMR spectra showing that it exists under CH-form in $CDCl_3$ and coexist under different forms with the proportional amount of OH-form > CH-form >> NH-form in DMSO-d_6.[4] Thus the yield of the chlorination reaction of **I** and preparation of 5-chloro-1,3-dimethylpyrazole can be affected by keto-enol tautomerism (Scheme 3).

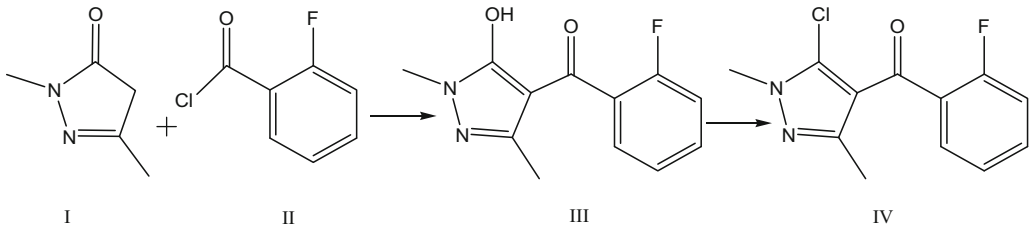
Herein, attempts have been made to the synthesis of **IV** *via* chlorination of **III** which has been synthesized *via* C-acylation of **I** by 2-fluorobenzoyl chloride (**II**) (Scheme 4). 1,3-dimethyl-5-pyrazolone (I) has been synthesized *via* solvent-less reaction of ethyl acetoacetate with methyl hydrazine under previously reported conditions.[4]

Although this procedure has been previously proposed for the synthesis of **IV** analogous compounds,[5–12] the synthesis of **IV** *via* this procedure has not been considered yet as much as the formation of cyclized side product **V** (Scheme 5), which has also been reported several times for the analogous compounds.[9,12,15,16]

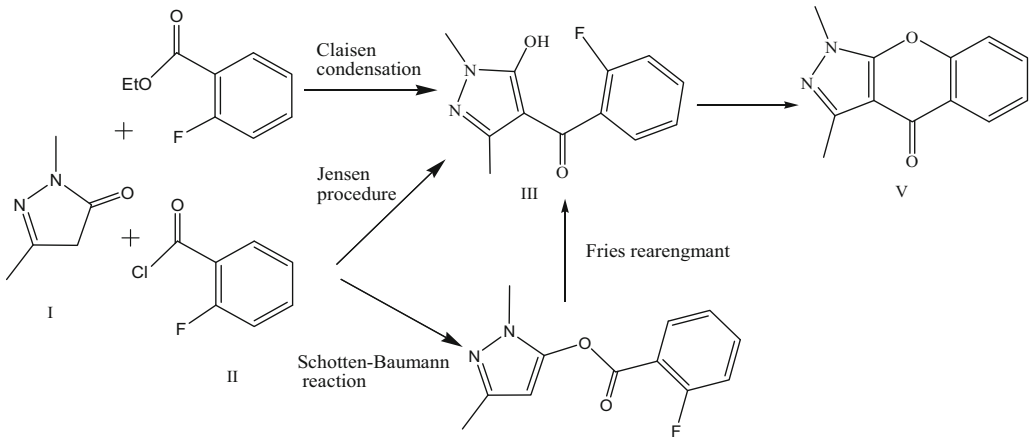
The compound **III** can also be prepared by Claisen condensation of ethyl-2-fluorobenzoate with **I** (catalyzed by sodium ethoxide); or by Schotten-Baumann reaction of **I** with **II** and Fries rearrangement of the produced O-acylated pyrazolone affording C-acylated product (Scheme 5). Both procedures suffer from the drawbacks such as low yields and colored side products. The preferred protocol (developed by Jensen[13] and intensively exploited) consists of direct acylation of **I** with **II** in the presence of calcium hydroxide. It has been stated that calcium hydroxide plays two crucial versatile roles: making the required pH needed to form the enol and complex formation with the hydroxyl functionality. Additionally, 2 equivalent of calcium hydroxide should be used to trap the liberated hydrogen chloride, and thus keep the media basic to avoid the decomposition of the complex during the acylation reaction.[6] Thus, it is very important to form the calcium complex before acylation. If the acylating agent is added immediately after calcium hydroxide, the corresponding O-acylated pyrazolones are the only or the main reaction product.[9] The synthesis of **III**



Scheme 3. Chlorination of tautomeric forms of 1,3-dimethyl—5-pyrazolone.



Scheme 4. Proposed method for the synthesis of **IV** *via* C-acylation of **I** by **II** and chlorination of the acylated product.



Scheme 5. Different ways for the synthesis of **III** and possible intermolecular cyclization.

following Jensen procedure ($Ca(OH)_2$, 1,4-dioxane) has been previously achieved with 47% yield.[15] The chlorination of compounds analogous to **III** has been performed under different conditions in $POCl_3$[10–12,14] but the preparation of **IV** *via* chlorination of **III** has not been investigated yet.

2. Experimental

2.1 *Chemicals and apparatus*

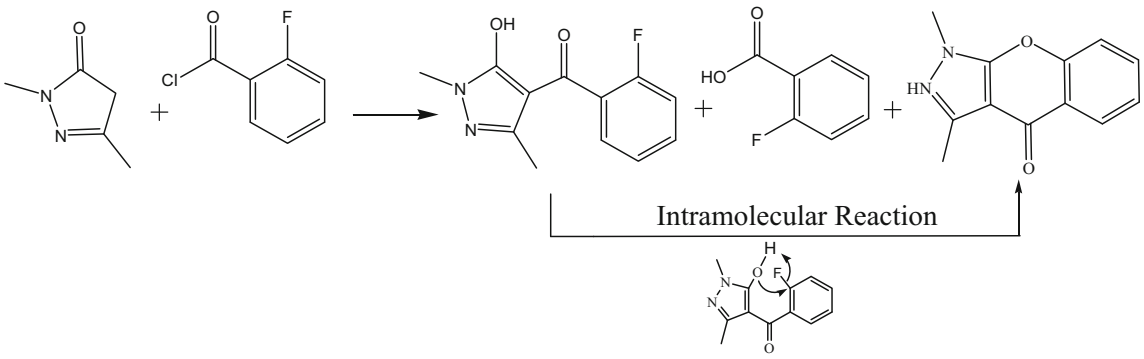
All solvents and chemical materials were of analytical grades (supplied by Aldrich and Merck) and were used without any further purification. NMR spectra were recorded by three instruments (Bruker Avance-300 and Bruker Ascend-400 spectrometer). $CDCl_3$ and DMSO-d_6 were used as solvents, the proton and carbon chemical shifts were recorded in δ (ppm) from TMS. Electronic ionization GC–MS spectra were recorded on a Agilent spectrometer (GC 7890B, GC-MSD 5977B) with a capillary column (HP-5MS UI, 0.25 μ, 30m_0.250 mm). Only m/z values having intensities of more than 20% are given, and retention times are reported using temperature programming (100–200 °C, 10 °C /min, 200 °C, 10 min, 200-280 °C, 20 °C /min) with a He flow rate of 1 mL/min.

2.2 *Synthesis of 1,3-dimethyl-5-pyrazolone (I)*

Ethyl acetoacetate (28.1 mL, 28.63 g, 0.22 mol) was placed in a 100 mL one necked flask equipped with a magnetic stir bar and immersed in an ice-water bath (0 °C). Then, methyl hydrazine (10.5 mL, 9.21g, 0.20 mol) was added dropwise (1 mL/min). After the addition of methyl hydrazine, flask cap has been tightly closed and the reaction mixture was stirred for 1 h at 80 °C, and for 30 min at 90 °C. Finally, water, ethanol and ethyl acetoacetate (excess) were vacuum stripped and the formed solids were washed with diethyl ether giving pale brown solids (22.4 g, R= ~100%) M.p. 113-117 °C. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.04 (s, 3H), 3.13 (s, 2H), 3.22 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 16.9, 31.0, 41.4, 155.6, 172.3.

2.3 *Synthesis of (5-hydroxy-1,3-dimethyl-1H-pyrazol-4-yl)(2-fluorophenyl)methanone (III)*

1,4-dioxane (150 mL) and 1,3-dimethyl-5-pyrazolone (**I**) (11.20 g, 0.10 mol) were placed in a 250 mL two necked flask equipped with a magnetic stir bar. The mixture was stirred for 15 min at 30 °C until complete dissolution of **I**. Then, $Ca(OH)_2$ (22.48 g, 0.30 mol)



Scheme 6. The targeted product (**III**) and principal side products (2-fluorobenzoic acid and tricyclic product (**V**)) in the acylation of **I** by **II**.

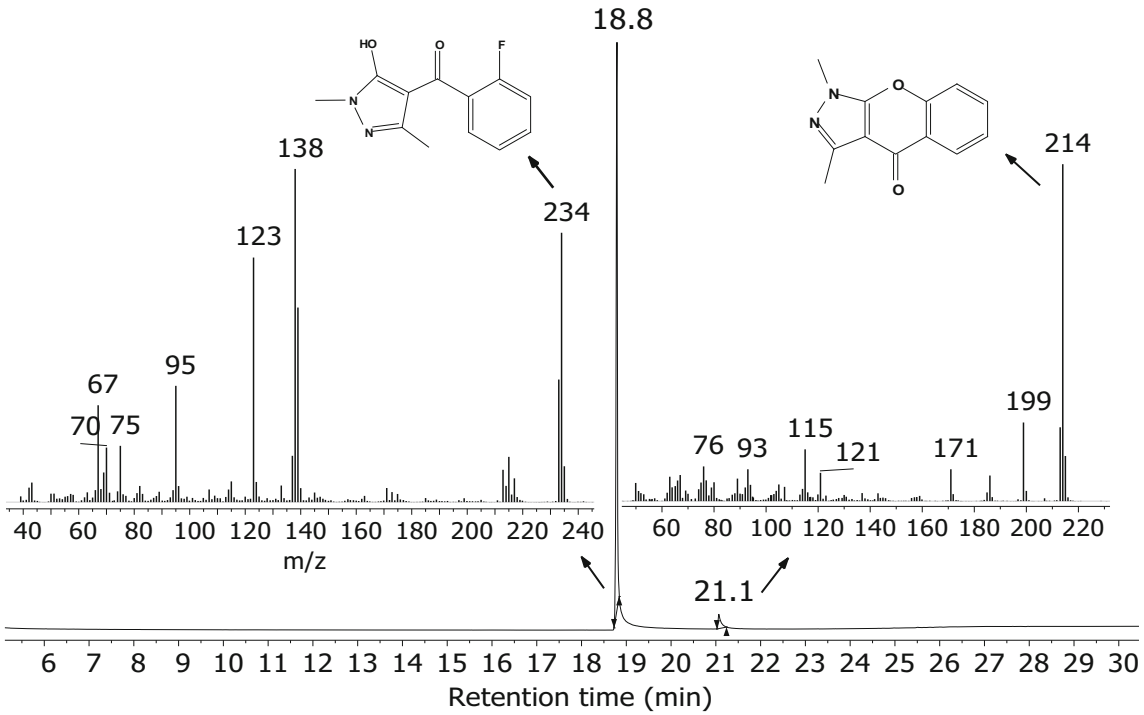


Figure 1. GC-MS analysis (chromatogram and fragmentation pattern) of purified **III** (99.5%) containing 0.5% of tricyclic side product (**V**).

was added to the flask and the reaction mixture was strongly stirred for 15 min at 80 °C until complete complex formation of the hydroxyl functionality of **I** with $Ca(OH)_2$. The temperature was then decreased to RT and a solution of 2-fluorobenzoyl chloride (**II**) (17.4 g, 0.11 mol, 13.1 mL) in dioxane (10 mL) was added dropwise after which the mixture was stirred for 18 h under reflux condition. Afterwards, the reaction mixture was cooled to RT and was stirred for another 1 h after the addition of HCl (2 N) (450 mL). Finally, chloroform (100 mL) was added to the reaction mixture and the organic layer was separated, washed with water and dried over $CaCl_2$. The solids obtained (17.35 g) after evaporation of solvent were washed with cold methanol (10 mL) and were recrystallized from methanol to give 14.78 g of pink pale crystals (63%): M.p. 153-155 °C (ref.[15], 153-155 °C); GC–MS (EI, 70 eV): Retention time: 18.8 min; (m/z) (%), 67 (29), 95 (34), 123 (73), 138 (100), 139 (58), 233 (36), 234 (80). ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.93 (s, 3H), 3.66 (s, 3H), 7.57-7.17 (m, 4H), 10.58 (s, OH).^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 13.93, 13.94, 32.69, 76.84, 77.16, 77.48, 103.74, 116.18, 116.39, 124.58, 124.61, 127.33, 127.49, 128.99, 129.02, 132.62, 132.70, 147.65, 157.66, 159.78, 160.14, 188.85.

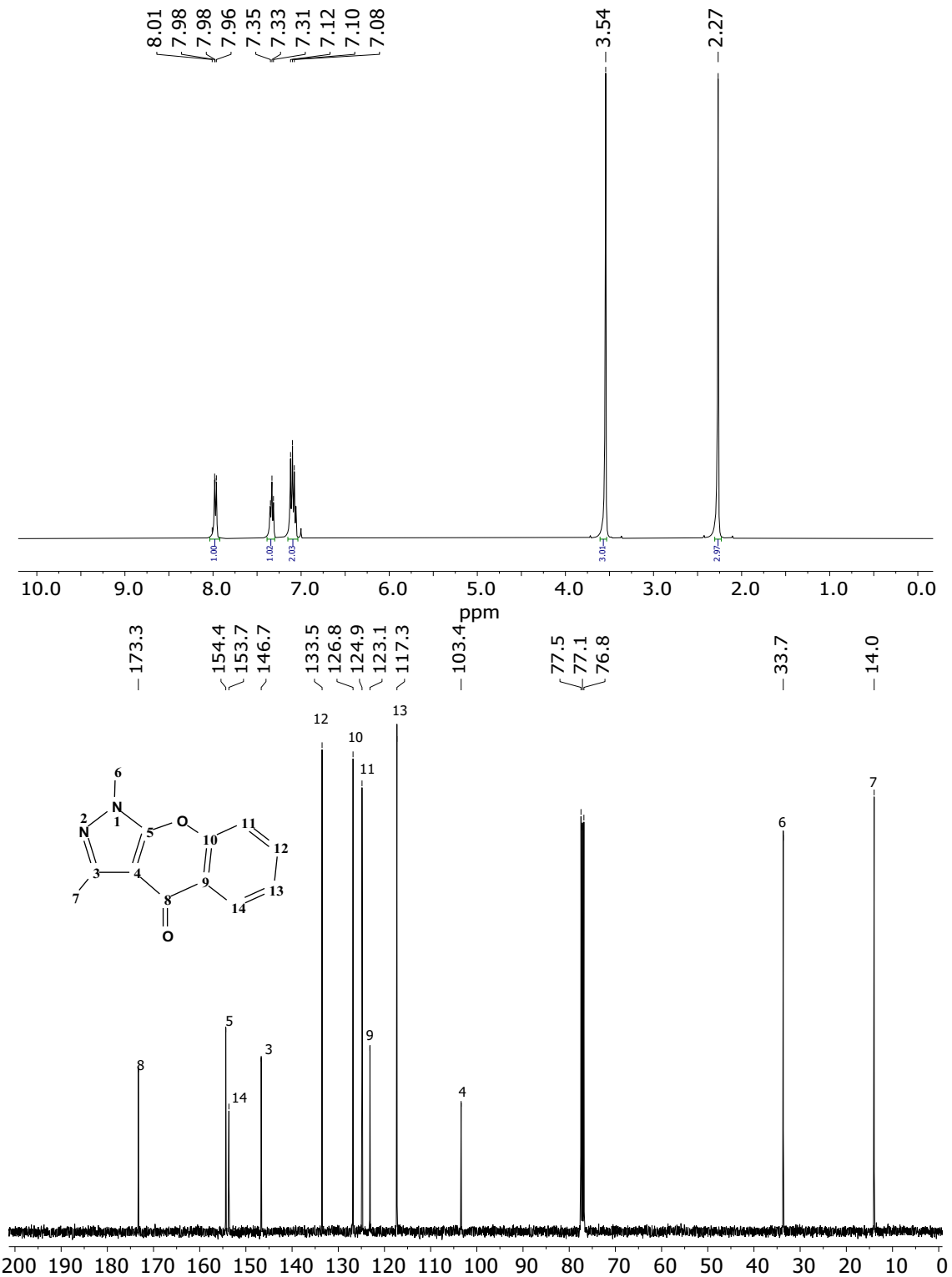


Figure 2. ^{1}H and ^{13}C NMR spectra of tricyclic side product (**V**).

2.4 *Synthesis of (5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)(2-fluorophenyl) methadone (IV)*

A mixture of $POCl_3$ (32.2 g, 0.21 mol, 19.5 mL) and (2-fluorophenyl)(5-hydroxy-1,3-dimethyl-1H-pyrazol-4yl) methanone (**III**) (3 g, 0.012 mol) (in a one necked flask equipped with a magnetic stir bar) was stirred for 6 h at 100 °C. Then, the cold reaction mixture was added dropwise to a mixture of ice and H_2O (100 g, with vigorous stirring). The organic layer was separated, washed

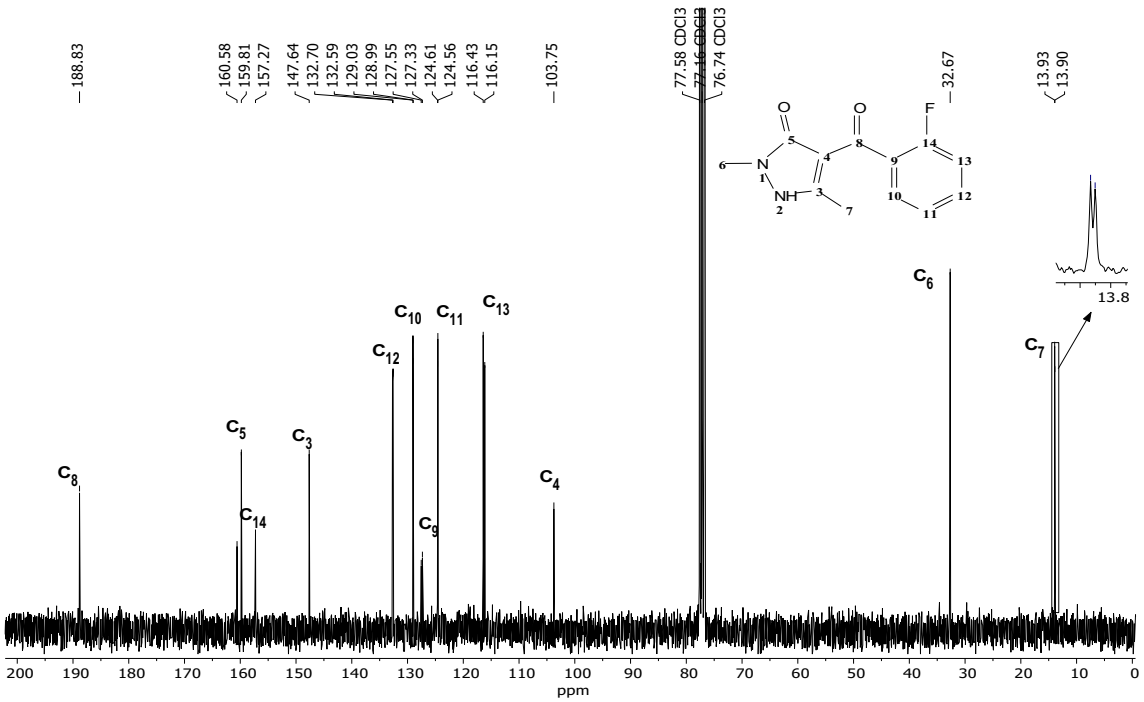


Figure 3. ^{13}C NMR spectra of **III** in $CDCl_3$.

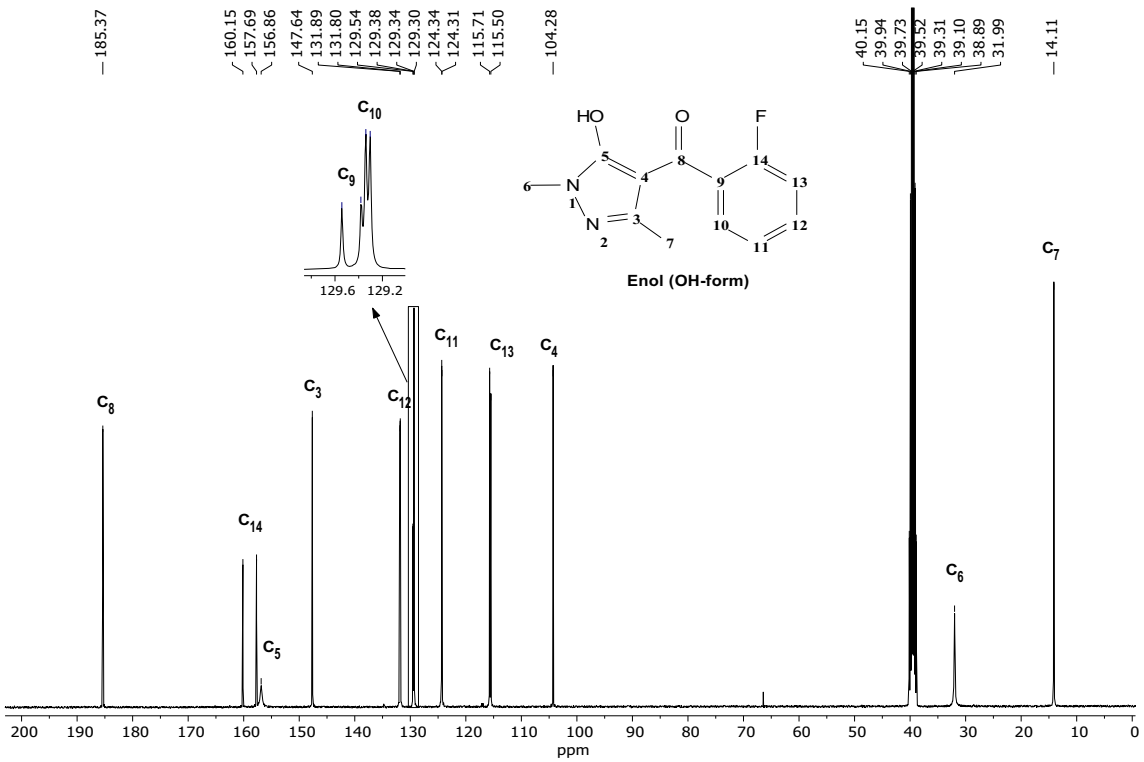
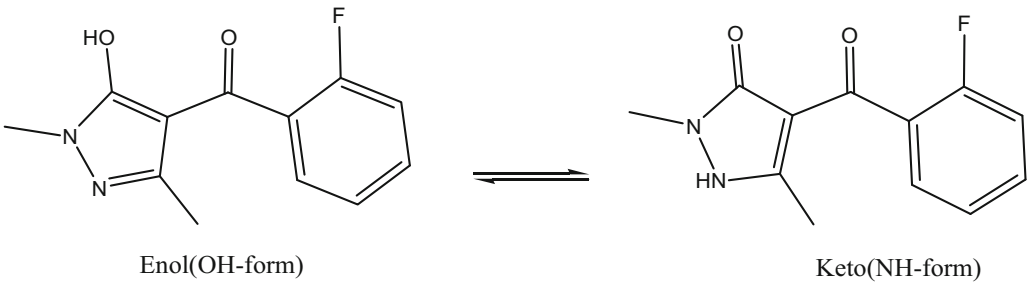


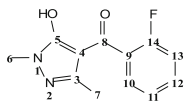
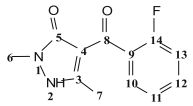
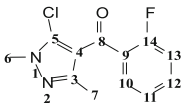
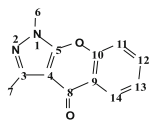
Figure 4. ^{13}C NMR spectra of **III** in DMSO-d_6.

with water (3 x 100 mL) and dried over $CaCl_2$. After solvent evaporation, the residue was washed with diethyl ether. Evaporation of diethyl ether afforded 2.25 g of white crystals (75%), M.p. 70–72 °C (ref.[3], 73-75 °C). GC–MS (EI, 70 eV): Retention time: 19.6 min; (m/z) (%), 75 (23), 76 (20), 95 (33), 157 (100), 159 (32), 233



Scheme 7. Keto-enolic tautomerization of **III**.

Table 1. Chemical shifts of carbons for **III**, **IV** and cyclic side product (**V**) and coupling constants of the aromatic carbon with fluorine ($J_{C\text{-}F}$ (Hz) for **III** and **IV**.

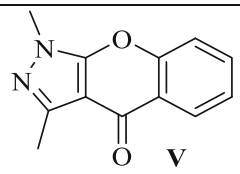
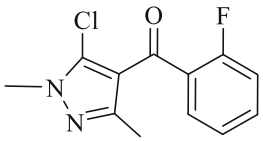
Molecule / Carbon No.	 III Enol (OH-form)	 III Keto(NH-form)	 IV	 Cyclic side product (V)
C_3	147.64	147.64	151.04	146.83
C_4	104.28	103.75	117.31	103.55
C_5	156.86	159.81	131.01	154.50
C_6	31.99	32.67	36.21	33.73
C_7	14.11	13.90 & 13.93	14.29	14.04
C_8	185.37	188.83	185.93	173.39
C_9	129.38 & 129.54 (J = 12.0 Hz)	127.33 & 127.55 (J = 16.5 Hz)	128.16 & 128.36 (J = 15.0 Hz)	123.32
C_{10}	129.30 & 129.34 (J = 3.0 Hz)	128.99 & 129.03 (J = 3.0 Hz)	129.91 &129.95 (J = 3.0 Hz)	126.96
C_{11}	124.31 & 124.34 (J = 2.2 Hz)	124.56 & 124.61 (J = 3.7 Hz)	124.41 & 124.46 (J = 3.7 Hz)	124.95
C_{12}	131.80 & 131.89 (J = 6.7 Hz)	132.59 & 132.70 (J = 8.2 Hz)	132.93 & 133.04 (J = 8.2 Hz)	133.56
C_{13}	115.50 & 115.71 (J = 15.7 Hz)	116.15 & 116.43 (J = 21.0 Hz)	115.86 & 116.15 (J = 21.7 HZ)	117.38
C_{14}	157.69 & 160.15 (J = 184.5 Hz)	157.27 & 160.58 (J = 248.2 Hz)	158.21 & 161.53 (J = 249.0 Hz)	153.84

(16), 251 (77), 252 (43), 253 (30). ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm) 2.38 (s, 3H), 3.83 (s, 3H), 7.11-7.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm) 14.29, 36.21, 76.74, 77.16, 77.58, 115.86, 116.15, 117.31, 124.41, 124.46, 128.16, 128.36, 129.91, 129.95, 131.01, 132.93, 133.04, 151.04, 158.21, 161.53, 185.93. The remaining pale green precipitates (0.67 g, 26%), after washing with diethyl ether, were cyclic side product with M.p. of 183-185 °C. GC–MS (EI, 70 eV): Retention time: 21.0 min; (m/z) (%), 198 (23), 212 (22), 214 (100). ^{13}C NMR (75 MHz, $CDCl_3$, δ ppm) 14.04, 33.73, 103.55, 117.38, 123.32, 124.95, 126.96, 133.56, 146.83, 153.84, 154.50, 173.39.

3. Results and Discussion

1,3-dimethyl-5-pyrazolone (**I**) has been quantitatively synthesized *via* the procedure that have been previously reported.[4] For the preparation of **III** following Jensen procedure ($Ca(OH)_2$, 1,4-dioxane), attention has been paid to ensure complete dissolution of **I** in 1,4-dioxane (carefully dried) before the addition of $Ca(OH)_2$ and complete complex formation of **I** with $Ca(OH)_2$ (at 80 °C, forming pink pale precipitates) after which 2-fluorobenzoyl chloride (**II**) (10% excess) was added dropwise at 0 °C. The addition of **II** before the complete complex formation of **I** with

Table 2. The weight (g) and yield (%) of **IV** and tricyclic side product (**V**) in the chlorination reaction of **III** (in 0.002 molar scale) under different reaction conditions (reaction time and temperature).

Row	Reaction Time	Reaction Temperature	 **V**	 **IV**
1	3 day	RT	0.01 (2%)	0.36 (68%)
2	6 day	RT	0.10 (18%)	0.35 (66%)
3	9 day	RT	0.08 (14%)	0.34 (64%)
4	3h	100 °C	0.01 (2%)	0.29 (54%)
5	6h	100 °C	0.12 (28%)	0.38 (70%)
6	9h	100 °C	0.10 (23%)	0.29 (58%)

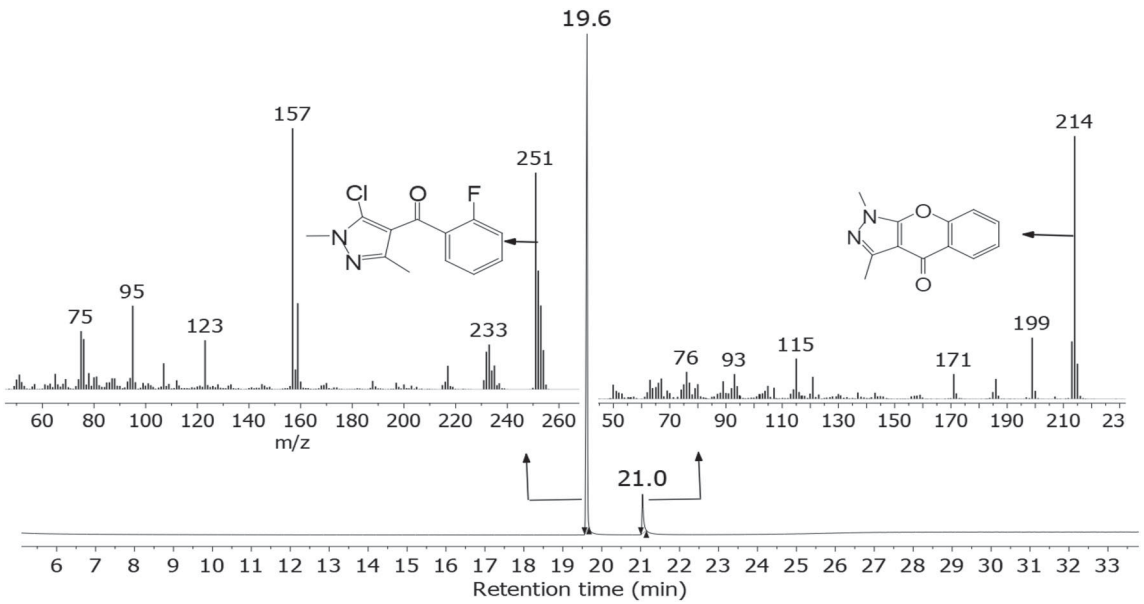


Figure 5. GC-MS analysis (chromatogram and fragmentation patterns) of purified **IV** (97.5%) containing 2.5% of tricyclic side product (**V**).

$Ca(OH)_2$ causes O-acylation (Schotten-Baumann reaction) which need a Fries rearrangement reaction to afford the targeted compound (**III**) (Scheme 5). Vigorous stirring is also needed during dropwise addition of hydrochloric acid (2N) at 0 °C in order to avoid coagulation of the products in the reaction mixture that prevents the decomposition of the complex and decrease the yield.

The reaction product **III** is prone to an intermolecular cyclization *via* the reaction of OH group of pyrazolone ring and fluorine atom of an adjacent phenyl group (Scheme 6) affording a tricyclic side product (**V**: 1,3-dimethylchromeno[2,3-c]pyrazol-4(1H)-one), a minor amount of which persist even after recrystallization, characterized *via* GC-MS analysis, ^{1}H and ^{13}C NMR spectroscopy (Figures 1 and 2). The major side product before recrystallization consists of 2-fluorobenzoic acid which is the hydrolysis product of **II** that perhaps occurs by the minor amount of water persisting in dioxane despite its careful drying by overnight heating under reflux over sodium wire. Thus, it is necessary to use a minimum amount of 1,4-dioxane as solvent (150 mL in the 0.1 molar scale) to allow minimum possible hydrolysis of **II** under reflux conditions.

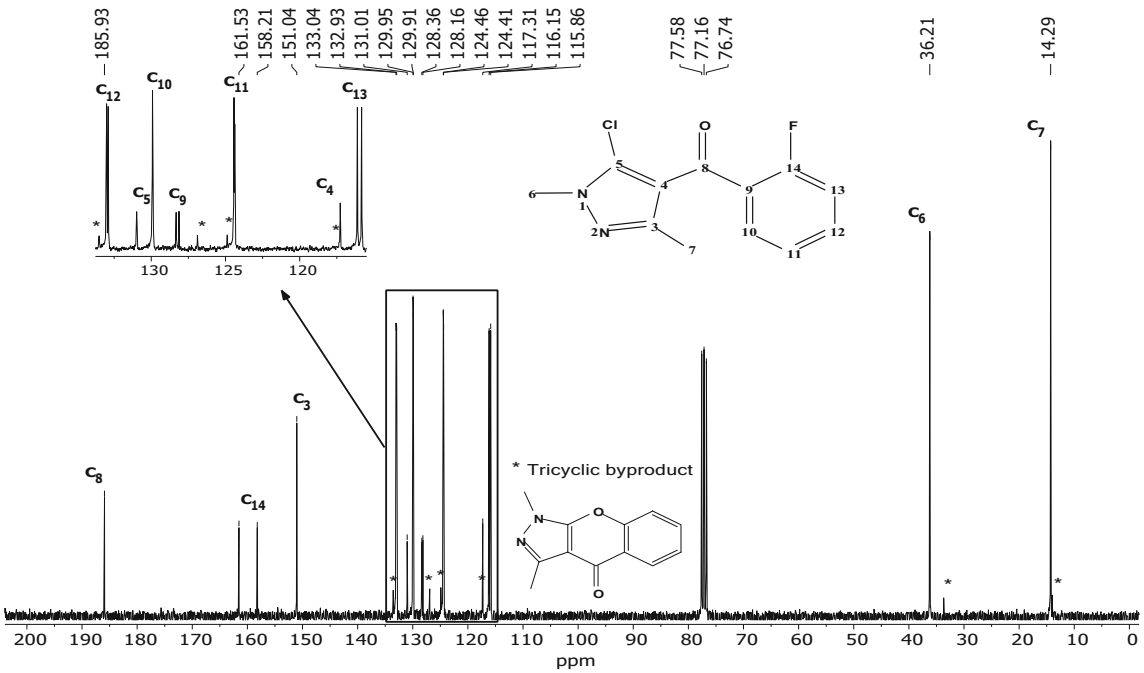


Figure 6. ^{13}C NMR spectra of purified **IV** (97.5%) containing 2.5% of tricyclic side product (**V**) in $CDCl_3$.

For the purification, the brut reaction product (after organic phase evaporation (dioxane and $CHCl_3$) is first washed with a minimum amount of cold methanol for dissolving the 2-fluorobenzoic acid (produced by hydrolysis of **II** in the course of reaction) before recrystallization in hot methanol. Under these conditions, a yield of 63% has been achieved while the previously reported yield for this reaction was 47%.

For investigation of keto-enol tautomerism, ^{13}C NMR (Figures 3 and 4) and ^{1}H NMR spectrum (Figures S1 and S2, Supplementary Information) of **III** were recorded using $CDCl_3$ and DMSO-d_6 as solvent. ^{13}C NMR spectra of **III** using DMSO-d_6 (Figure 4) showed two broadened peaks for C_6 (N-CH_3) and C_5 (C-OH) of the pyrazolone ring perhaps due to the hydrogen exchange properties of enol (OH-form) exerting also a downfield effect on C_9 ($\sim$2 ppm) and an upfield effect on C_8 ($\sim$3.5 ppm) compared to the same peaks in $CDCl_3$. In the other part, ^{1}H NMR spectra of **III** in DMSO-d_6 (Figure S2, Supplementary Information) present a symmetric peak at a chemical shift, δ, of $\sim$11.4 ppm, attributed to the hydrogen of hydroxyl group in the **III** under enol(OH-form) (Scheme 7).

^{13}C NMR spectra of **III** in $CDCl_3$ (Figure 3) showed a doublet peak for C_7 (carbon of methyl, C-CH_3) of the pyrazolone ring and ^{1}H NMR spectrum of **III** in $CDCl_3$ present an asymmetric pick at $\sim$10.6 ppm and more complex aromatic picks (7.20-7.50 ppm) compared to the same peaks in the spectra of **III** in DMSO-d_6. These two events can be perhaps attributed to the presence of two different conformers of **III** under keto(NH-form) in DMSO-d_6. The chemical shifts of other carbons and also coupling constants of the aromatic carbon with fluorine ($J_{C\text{-}F}$ (Hz); Table 1) conform to those predicted by MestReNova software and to the structure of **III** under the two tautomeric forms. This type of tautomerism has been previously reported for 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone.[17]

The chlorination of **III** to achieve **IV** has not been previously reported. This reaction has been performed using $POCl_3$ as chlorinating agent. Herein also, the tricyclic compound is present in the final reaction mixture as a side product. Thus different temperatures and reaction times have been examined to prevent the formation of tricyclic side products and to achieve **IV** with a high yield (Table 2). The minimum amount of tricyclic side product (2%) has been formed when the reaction has been performed in 3 days at RT (or in 3 h at 100 °C). Raising the reaction time, at RT or 100 °C, for obtaining a higher yield of targeted compound (**IV**) caused a higher amount formation of cyclized side product (**V**). Thus, the higher yield of the chlorination of **III** by $POCl_3$ (70%) has been achieved after 6 h at 100 °C. Diethyl ether has been found to be adequate solvent for recrystallization of 5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)(2-fluorophenyl) methanone (**IV**) and

separation of tricyclic side product (**V**) to a maximum amount. GC-MS analysis (chromatogram and fragmentation patterns) and ^{13}C spectra of purified IV (97.5%) containing 2.5% of tricyclic side product (**V**) are presented in Figures 5 and 6. ^{1}H NMR spectra of **IV** is presented in the Supplementary Information file (Figure S3, SI).

4. Conclusions

A new approach was developed for the synthesis of two important intermediates (III and IV) in the synthesis of zolazepam and the procedures were optimized to obtain pure high yielded products characterized by GC-MS and NMR spectroscopy. Attempts have been made to minimize the formation of tricyclic side product (**V**). Some tautomeric aspects of the acylated product III was also investigated by studying ^{1}H and ^{13}C NMR spectra in $CDCl_3$ and DMSO-d_6.

Supplementary Information (SI)

^{1}H NMR spectrum of **III** in $CDCl_3$ (Figure S1) and DMSO-d_6 (Figure S2) are available at www.ias.ac.in/chemsci.

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