

Intramolecular N to N acyl migration in conformationally mobile 1'-acyl-1-benzyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline] systems promoted by debenzylation conditions (HCOONH₄/Pd/C)

Research Article

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Abstract: We report an efficient and useful synthesis of new attractive spiroperidine scaffolds **4** based on an intramolecular acyl transfer process in 1'-acyl-1-benzyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **3** using simple and mild debenzylation reaction conditions (HCOONH₄/Pd/C). The compounds **3** were prepared by acylating 1-benzyl-4'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **2** that are easily available from 1-benzyl-4-piperidone **1**. The intramolecular character of this process was proven primarily through a crossover experiment technique. Through an examination of all spectroscopic information (¹H, ¹³C NMR, VT-¹H NMR, and ²D NMR) it was possible to correctly predict amide configurations and piperidine ring conformations of starting and final spiroperidine compounds.

Keywords: Spiropiperidines • 1'-Acyl-1-benzyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] • Intramolecular acyl transfer process • Debzylolation reaction

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1. Introduction

Intra- and intermolecular transfer processes of one chemical group (acyl, amine, amide etc) as a part of a molecule (donor) to another one (acceptor) are very important in organic chemistry and bioorganic chemistry, where they play a pivotal role in normal cellular function [1-4]. Among these transfer reactions, the acyl (acetyl) group transfer of organic molecules, both synthetic and natural, is studied more often. In the biological processes, this is usually an intermolecular reaction catalyzed by acetyltransferases [5,6], which can detoxicate xenobiotics or drugs by a N-acetylation reaction [7-10]. In the organic investigations, acyl transfer reactions were, and still are, objects of discussion of possible mechanisms. Moreover, the studies on N-N acyl migration limit with simple substrates, e.g. fenolates and phenyl acetates [11-13]

or isoquinoline and pyridine derivatives [14] and do not focus on synthetic aspects of these types of the organic reactions. In contrast, intramolecular O-N acyl migration reactions are more used in the synthesis of complex substrates both in organic and medicinal chemistry [15-17].

On the other hand, the piperidine ring is the commonest heterocyclic unit of many alkaloids, and is a key part of numerous drug candidates, this is why research in piperidine chemistry and synthesis continues to be prominent [18]. It was reported that during a decade (1988-1998) there were over 12.000 piperidine compounds mentioned in clinical and preclinical studiem, and among them, 1,4-disubstituted piperidines dominated [19]. Thus, it is not surprising that the chemical literature reveals an increasing number of publications on these derivatives with varied biological activities.

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Among diverse simple piperidine derivatives 1-benzyl-4-piperidone has been used as starting material en route to a considerable number of piperidine drugs. 1-benzyl-4-piperidone continues to be very useful and important starting material because of its availability, physical stability, chemical reactivity, and low cost, due to the *N*-benzyl moiety as latent protector group. The benzyl moiety is one of the most commonly employed protecting groups for the heteroatom functionality in organic synthesis. Deprotection of *N*-benzyl group by catalytic transfer hydrogenolysis is a safe and simple operation between a catalyst and hydrogen gas or another hydrogen donor [20]. Spiropiperidine derivatives are also important piperidine scaffolds in the drug development. For instance, some 1'H-spiro[piperidine-4,2'-quinolines] **A** or 4',4'-dimethyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **B** were designed as potential antioxidant agents [21]. The spiro system of 3'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline] **C**, where the spiranic center is the carbon adjacent to the phenylamine nitrogen, also shows interesting features that make it attractive for synthetic and pharmacological use [22,23] (Fig. 1).

We report herein an efficient and useful synthesis of new attractive spiro-piperidine scaffolds based on an intramolecular acyl transfer process in 1'-acyl-1-benzyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] using simple and mild benzylation reaction conditions (HCOONH₄/Pd/C), we also discuss spatial piperidine structures deduced from careful spectroscopic data analysis and our logical steps to propose a plausible mechanism of the intramolecular N-N acyl transfer reactions in a conformationally mobile 1'-acyl-1-benzyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline] system.

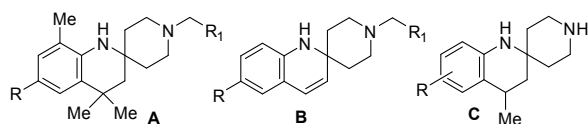
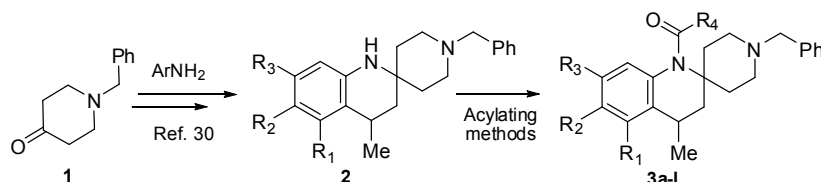


Figure 1. Compounds with spiro[piperidine-4,2'-quinoline] skeleton as possible pharmaceuticals.



Acylating methods: a. HCOOH/Ac₂O/Py/0°C; b. Ac₂O/NEt₃/Δ; c. PhCOCl/NEt₃/PhMe/r. t.; d. MeCOCl/NEt₃/CH₂Cl₂/0°C; e. *p*-NO₂C₆H₄COCl/NEt₃/PhMe/5°C.

Scheme 1. Preparation of starting acyl derivatives **3**.

2. Experimental procedure

2.1. General

The general route for the synthesis is shown in Scheme 1.

2.1.1 Formylation

(Compounds **3a**, **3d**, **3i**, **3k**). A solution of Ac₂O (2.00 mmol), HCOOH (3.00 mmol) and two drops of pyridine was added to the respective 1-benzyl-4'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **2** (1.00 mmol) at 0°C. The reaction mixture was stirred for 0.5-1 h at the same temperature. Then, the reaction mixture was treated with NH₄OH to get a pH 7-8, and then it was extracted with CH₂Cl₂ (3×10 mL). Organic extracts were washed with water and dried over Na₂SO₄, concentrated, then purified by column chromatography on neural alumina, using heptane–ethyl acetate mixture (15:1, 10:1, 5:1) as an eluent.

2.1.2 Acetylation

(Compounds **3b** and **3e**). A mixture of the respective 1-benzyl-4'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **2** (1.00 mmol) and Ac₂O (3.00 mmol) was refluxed for 1-2 h in the presence of NEt₃ (two drops). Then, reaction mixture was treated with NH₄OH to get a pH 7-8, and then it was extracted with CH₂Cl₂ (3×10 mL). Organic extracts were washed with water and dried over Na₂SO₄, concentrated, then purified by column chromatography on neural alumina, using heptane–ethyl acetate mixture (15:1, 10:1, 5:1) as an eluent.

2.1.3 Benzoylation

(Compounds **3c** and **3f**). A solution of PhCOCl (2.00 mmol) in dry toluene (10 mL) was dropped slowly to the solution of the respective 1-benzyl-4'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **2** (1.00 mmol) and NEt₃ (1.00 mmol) in dry toluene (20 mL) at 0°C. The reaction mixture was stirred for 2-3 h at the room temperature. Then, the reaction mixture was treated with NH₄OH to get a pH 7-8, and

then it was extracted with CH_2Cl_2 (3×10 mL). Organic extracts were washed with water and dried over Na_2SO_4 , concentrated, then purified by column chromatography on neural alumina, using heptane–ethyl acetate mixture (15:1, 10:1, 5:1) as an eluent.

2.1.4 Chloroacetylation

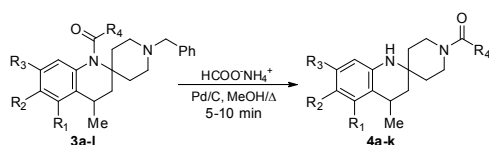
(Compounds **3g** and **3l**). A solution of ClCH_2COCl (2.00 mmol) in dry CH_2Cl_2 (10 mL) was dropped slowly to the solution of the respective 1-benzyl-4'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **2** (1.00 mmol) and NEt_3 (1.00 mmol) in dry CH_2Cl_2 (20 mL) at 0°C . The reaction mixture was stirred for 1–2 h at the same temperature. Then, the reaction mixture was treated with NH_4OH to get a pH 7–8, and then it was extracted with CH_2Cl_2 (3×10 mL). Organic extracts were washed with water and dried over Na_2SO_4 , concentrated, then purified by column chromatography on neural alumina, using heptane–ethyl acetate mixture (15:1, 10:1, 5:1) as an eluent.

2.1.5 Nitrobenzoylation

(Compound **3h**). A $p\text{-NO}_2\text{PhCOCl}$ (1.73 g, 9.30 mmol) was added in small portions to the solution of 1-benzyl-4'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinoline] **2a** (1.49 g, 4.65 mmol) y NEt_3 (0.46 g, 1 mmol) in dry toluene (20 mL) at 0°C . After 5 min, reaction mixture was treated with NH_4OH to get a pH 7–8, and then it was extracted with CH_2Cl_2 (3×10 mL). Organic extracts were washed with water and dried over Na_2SO_4 , concentrated, then purified by column chromatography on neural alumina, using heptane–ethyl acetate mixture (15:1, 10:1, 5:1) as an eluent.

2.2 Typical experimental procedure for synthesis of 1-acyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **4a-k**

A mixture of compound **3** (1.00 mmol), HCOONH_4 (315.3 mg, 5.00 mmol) and 2.5% molar amounts of 10% Pd/C was refluxed in methanol (20 mL) for 7–15 min. The reaction mixture was filtered and the solvent was taken off. Crude products **4** were purified by alumina column chromatography using ethyl acetate or ethyl acetate-methanol mixture (10:1, 5:1, 2:1 or 1:1) as eluents (Scheme 2).



Scheme 2. Preparation of new 1-acyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **4**.

All data for the synthesized compounds **3,4** are presented in Supplementary Information.

3. Results and discussion

The main materials, - 1-benzyl-4'-methyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **2** are easily available from commercial and cheap 1-benzyl-4-piperidone **1**. Simple acylation reactions of these piperidine compounds give the corresponding the 1'-acyl-1-benzyl-3',4'-dihydro-1'H-spiro[piperidine-4,2'-quinolines] **3a-l** in excellent yields. All N-amides **3** are solid or oil substances. Their structure was confirmed by IR and GC-MS data. Mass spectra of the compounds **3a-l** showed molecular ion with very poor intensity (0.5–8.0%) (Table 1 and Supplementary Table 1).

Since acyl spiranes are complex conformationally mobile systems their facile preparation and MS analysis differs significantly from the structural characterization by the NMR. Their ^1H NMR spectra have confused aliphatic zones that become considerably cleaner when the chemical nature of the amide group is changing (from formyl to benzoyl). For example, spectra of formamides **3a,d,i,k** ($R_4 = \text{H}$) showed signals as a broad singlet without any resolution, one of acetamides **3b,e** ($R_4 = \text{CH}_3$) and chloroacetamide **3g,l** ($R_4 = \text{CH}_2\text{Cl}$) indicated a better resolution and spectra of benzoyl derivatives **3c,f** ($R_4 = \text{C}_6\text{H}_5$) and p -nitrobenzoyl derivative **3h** ($R_4 = 4\text{-NO}_2\text{-C}_6\text{H}_4$) presented clear and separate signals of each aliphatic piperidine protons. For example, the ^1H NMR spectrum of benzamide **3c** showed a nice picture with 8 signals for piperidine ring and 4 signals for dihydroquinoline moiety (see, Supplementary Fig. 1). The piperidine signals had the following characteristics: axial and equatorial 3-H hydrogens appeared at 1.36 and 3.29 ppm as doublet doublets with vicinal coupling constants $J = 12.5, 2.3$ Hz and $J = 12.7, 4.5$ Hz, respectively; axial and equatorial 5-H hydrogens were located at 1.57 ppm (doublet doublets, $J = 12.8, 2.3$ Hz) and at 3.34 ppm (triplet doublets, $J = 12.2, 4.1$ Hz), respectively; axial and equatorial 4-H hydrogens resonated at 2.06 ppm (triplet doublets, $J = 12.0, 2.3$ Hz) and at 2.81 ppm (triplet doublets, $J = 11.7, 2.0$ Hz), respectively. Finally, axial and equatorial 6-H hydrogens appeared at 2.38 and 2.94 ppm as triplet doublets with the corresponding vicinal constants $J = 12.0, 2.9$ Hz and $J = 11.8, 2.3$ Hz. The dihydroquinoline protons gave the following characteristics: triplet doublets ($J = 12.8, 1.2$ Hz) at 1.07 ppm belonging to the axial 3'-H hydrogen, doublet doublets ($J = 12.9, 3.0$ Hz) at 2.54 ppm for the equatorial 3'-H hydrogen and a sextet ($J = 6.7$ Hz) at 2.89 ppm was generated by a 4'-H proton. It should be

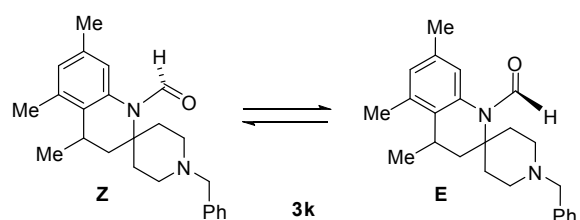
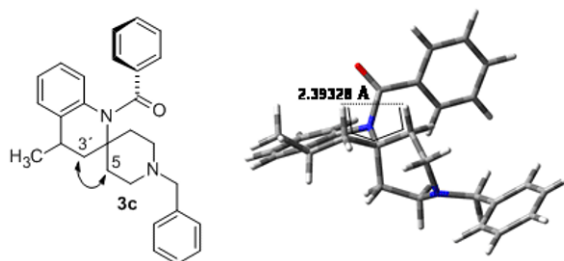
Table 1. Physicochemical characteristics of **3**.

Comp.	R ₁	R ₂	R ₃	R ₄	Condensed Formula	Weight (g mol ⁻¹)	GC: t _R (min)	M ⁺	IR ν _{N-C=O} (cm ⁻¹)	Mp, °C	Yields, %
3a	H	H	H	H	C ₂₂ H ₂₆ N ₂ O	334.46	49.13	334 (1)	1676	oil	95
3b	H	H	H	CH ₃	C ₂₃ H ₂₈ N ₂ O	348.48	44.09	348 (5)	1657	oil	89
3c	H	H	H	C ₆ H ₅	C ₂₆ H ₃₀ N ₂ O	410.55	42.67	-	1648	124-125	82
3d	H	CH ₃	H	H	C ₂₃ H ₂₈ N ₂ O	348.48	53.99	348 (1)	1677	90-91	85
3e	H	CH ₃	H	CH ₃	C ₂₄ H ₃₀ N ₂ O	362.51	47.45	362 (8)	1663	26-27	86
3f	H	CH ₃	H	C ₆ H ₅	C ₂₉ H ₃₂ N ₂ O	424.58	45.89	-	1641	oil	81
3g	H	CH ₃	H	CH ₂ Cl	C ₂₄ H ₂₉ ClN ₂ O	396.95	36.24	396 (1)	1669	119-120	89
3h	H	CH ₃	H	C ₆ H ₄ NO ₂ -p	C ₂₉ H ₃₁ N ₃ O ₃	469.58	30.74	-	1648	147-148	70
3i	H	F	H	H	C ₂₂ H ₂₅ FN ₂ O	352.45	30.25	352 (0.5)	1666	oil	90
3k	CH ₃	H	CH ₃	H	C ₂₄ H ₃₀ N ₂ O	362.61	33.49	362 (1)	1660	oil	100
3l	CH ₃	H	CH ₃	CH ₂ Cl	C ₂₅ H ₃₁ ClN ₂ O	410.98	36.81	-	1668	158-159	79

mentioned that despite of many studies on simple acyclic amide conformational aspects [24-26], conformational analysis of *N*-acyl bond rotation in the *N*-heterocyclic systems is very complex, and still poorly investigated [26]. In our case of *N*-acyl spiro derivatives **3** obtained, the situation is also complex and confusing. This is due to two different phenomena of amide rotation and piperidine ring inversion. From ¹³C NMR data analysis for the formamides **3a,d,i,k** (R₄ = H) one could see a duplication of each of the carbon atoms. Moreover, the ¹H NMR spectra of the formamides **3a,k** showed two signals of N-C(O)H proton; in the case of compound **3k** these signals resonated separately enough to calculate its 2.5:1 ratio (Fig. 2).

From early ¹H NMR studies simple *N*-methyl- and *N*-ethylformamides strong preference for the *Z*-isomer (*N*-bulkier group anti to carbonyl oxygen) is known to exist [25]. Thus, this information and our findings permit us to believe that the major isomer of amides **3** has a *Z*-favored form. Additional information on conformational aspects of these new *N*-acyl derivatives was obtained from correlation spectroscopy (COSY) experiments. In the spectra of the compounds **3c** and **3f** a cross-peak between a 3'-Ha dihydroquinoline proton and a 5-He piperidine proton was observed, those long-range coupling constants ⁴*J* were 1.2 Hz. Molecular modeling studies on the benzamide **3c** performed by the Gaussian program [27] were in agreement with the reported NMR observations, and a *W*-configuration in forced rigid molecular architecture of these derivatives was suggested. Both the experiment and calculation results allowed us to propose a possible geometry of more stable *Z*-conformer of the benzamide **3c**, where its dihydroquinoline ring adopts a semi-chair form and the piperidine has a twisted boat (Fig. 3).

¹H NMR and ¹³C NMR spectra analysis of the acylated spiro products **3** showed no observation of conformers signals for the acetamides and benzamides


Figure 2. *Z*- and *E*-isomers of formamide **3k**.

Figure 3. Capped-stick model of lowest energy of compound **3c**.

indicating that these signals can coalesce at room temperature. It is important to note that during ¹H NMR and ¹³C NMR spectra analysis of these compounds we could not observe the process of *N*-benzylpiperidine ring inversion.

After the characterization of amide series **3**, *N*-*N* acyl migration process was studied under debenzilation conditions. All these amides were treated with an excess of ammonium formate in refluxing methanol in the presence of 10% Pd/C for 5-20 min. With these mild reaction conditions and the classical work-up exclusive rearranged products **4** were obtained in excellent yield as white (or yellow) crystalline high-melting solids (Table 2). Structural elucidation of all the *N*-acylpiperidine derivatives **4a-k** was realized in the same order using set of the spectroscopic and spectrometric techniques. It should be mentioned that during the *N*-*N* acyl migration reaction of **3a-l**, all functionalities were intact except for the amides **3g,l** (R₄ = CH₂Cl) and **3h** (R₄ = C₆H₅NO₂-p),

Table 2. Physicochemical properties of **4**.

Comp.	R ₁	R ₂	R ₃	R ₄	Condensed Formula	Weight (g mol ⁻¹)	GC: t _R (min)	M ⁺	IR _{N-H, N-C=O} ^v (cm ⁻¹)	Mp, °C	Yields, %
4a	H	H	H	H	C ₁₅ H ₂₀ N ₂ O	244.33	32.89	244 (98)	3388/1676	153-154	93
4b	H	H	H	CH ₃	C ₁₆ H ₂₂ N ₂ O	258.36	33.71	258 (61)	3348/1623	136-137	96
4c	H	H	H	C ₆ H ₅	C ₂₁ H ₂₄ N ₂ O	320.43	31.79	320 (47)	3437/1645	106-107	90
4d	H	CH ₃	H	H	C ₁₆ H ₂₂ N ₂ O	258.36	34.28	258 (100)	3394/1679	168-169	91
4e	H	CH ₃	H	CH ₃	C ₁₇ H ₂₄ N ₂ O	272.39	35.34	272 (67)	3354/1635	114-115	88
4f	H	CH ₃	H	C ₆ H ₅	C ₂₂ H ₂₆ N ₂ O	334.46	33.75	334 (48)	3420/1641	155-156	75
4g	H	CH ₃	H	C ₆ H ₄ NH ₂ -p	C ₂₂ H ₂₇ N ₃ O	349.47	36.78	349 (8)	3471, 3338, 3212/1622	147-148	92
4h	H	F	H	H	C ₁₅ H ₁₉ FN ₂ O	262.32	23.21	262 (100)	3343/1665	160-161	97
4i	CH ₃	H	CH ₃	H	C ₁₇ H ₂₄ N ₂ O	272.38	24.81	272 (82)	3343/1669	104-105	98
4k	CH ₃	H	CH ₃	CH ₃	C ₁₈ H ₂₆ N ₂ O	286.41	25.45	286 (40)	3405/1657	169-170	100

Table 3. Conformer ratio of obtained N-formyl(acetyl) piperidine derivatives **4**.

Compound	δ, ppm	Signals			
		A H-C=O	B H-C=O	A CH ₃ -C=O	B CH ₃ -C=O
4a	8.05/8.04	1	0.88		
4b	2.12/2.10			1	0.84
4d	8.05/8.03	1	0.88		
4e	2.11/2.10			1	0.84
4h	8.05/8.04	1	0.88		
4i	8.04/8.03	0.96	1		

both of which were converted into rearranged products **4b,k** (R₄ = CH₃) and **4g** (R₄ = C₆H₅NH₂-p), respectively. It was easily proven by IR and GC-MS data (Table 2).

Analyzing ¹H and ¹³C NMR data for formamides **4a,d,h,i** and acetamides **4b,e** we clearly observed two isomers generated by amide C-N bond rotation. We were also able to analyze the ratio of presented amide rotation isomers **A** (*syn*) and **B** (*anti*) for these types of amides that were found using formyl and acetyl protons in room temperature solution (Table 3).

To study this phenomenon at greater length, we carried out diverse dynamic (variable temperature) VT-NMR experiments [28,29] in two solvents, - CDCl₃ and C₃D₃O ([D6]acetone) of the acetamide **4e**. CDCl₃ solution VT ¹H NMR experiments were conducted at five degree intervals between -40 and +40°C (see Supplementary Fig. 6), and the results showed that as the temperature grows, the σ v values between two singlets of the Me amide group considerably decrease (Table 4). Since coalescence could not be observed, it would suggest that these signals and conformers will coalesce at the temperature higher than 40°C.

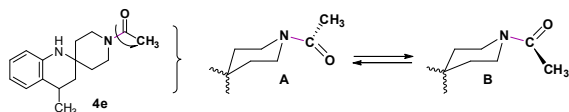
C₃D₃O solution VT ¹H NMR experiments were conducted at five or ten degree intervals between -65 and +20°C (see, Supplementary Fig. 7). With the temperature decrease, very complex signals (δ 3.89-

3.79 ppm) of the piperidine 2-He proton converted into two independent signals, when the temperature is higher than -25°C a broad signal at -65°C appeared (Table 5). This phenomenon is very different from the one discussed above: at this temperature, the amide C-N bond rotation process stops being significant and the coalescence strongly indicates at a piperidine ring inversion.

Analyses of the information obtained from dynamic ¹H NMR experiments suggest two dynamic processes: amide C-N bond rotation and piperidine ring inversion in the *N*-acetyl(formyl) piperidine series. Assignments of all piperidine protons were based on COSY cross coupling. These processes are shown in Scheme 3.

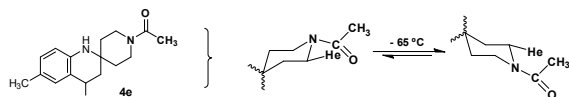
Generally, C-4 substituted *N*-acetylpiperidines adopt *syn* conformation and its *syn* rotamer can be easily identified by deshielded piperidine 2(6)-He protons [26,30-32]. In our case, the similar *N*-acetylpiperidine derivative **4e** presented two rotamers, *syn* and *anti*, from ¹H NMR study *syn* rotamer was found to be major. Moreover, using a ¹H-decoupled ¹³C MNR experiment (T = 25°C, time between scans: 20 sec., total scans - 1024) (see Supplementary Fig. 8), it was possible to find a rotamer ratio for this acetamide (1:0.81), which is very similar to ratio found from ¹H NMR spectrum (1:0.84, Table 3).

Table 4. Observation of amide rotamers **4e** by dynamic ¹H NMR (CDCl₃).



T, °C	δ ppm, CH ₃	δ ppm, CH ₃	δν, ppm
40	2.110	2.096	0.014
35	2.113	2.096	0.017
30	2.115	2.097	0.018
25	2.116	2.098	0.018
20	2.119	2.099	0.020
15	2.121	2.101	0.020
10	2.124	2.104	0.020
5	2.126	2.106	0.020
0	2.129	2.108	0.021
-10	2.136	2.114	0.022
-20	2.142	2.120	0.022
-30	2.178	2.155	0.023
-40	2.155	2.132	0.023

Table 5. Observation of piperidine conformers **4e** by dynamic ¹H NMR (J, Hz, C₃D₃O).



T, °C	2-He, δ, ppm	2-He, δ, ppm	δν, ppm
25	3.83 ddd (13.7, 10.7, 5.1 Hz)	3.76 ddd (13.3, 10.5, 5.5 Hz)	0.070
15	3.83 ddd (13.5, 10.6, 3.8 Hz)	3.76 ddd (13.5, 10.3, 3.7 Hz)	0.071
5	3.84 ddd (13.5, 10.5, 5.2 Hz)	3.77 ddd (13.3, 10.2, 5.0 Hz)	0.071
-5	3.85 ddd (13.5, 10.5, 5.2 Hz)	3.78 ddd (13.3, 10.3, 4.9 Hz)	0.072
-15	3.85 ddd (13.6, 10.4, 4.9 Hz)	3.78 ddd (13.3, 10.1, 4.9 Hz)	0.072
-25	3.86 ddd (13.7, 10.1, 4.8 Hz)	3.79 ddd (13.4, 10.0, 5.0 Hz)	0.071
-35	3.81 ddd (13.7, 9.7, 4.8 Hz)	3.87 ddd (13.7, 9.3, 4.4 Hz)	0.065
-45	3.81 bd (13.2 Hz)	3.88 bd (13.4 Hz)	0.071
-55	3.89 bd (12.2 Hz)	3.83 bd (12.0 Hz)	0.067
-65	3.87 bs		-
-75	3.88 bs		-

In order to elucidate this type of acyl migration process, which could be inter- or intramolecularly processed, a number of diverse experiments were conducted. Crude reaction mixture of the debenzoylation process for all starting compounds was analyzed by

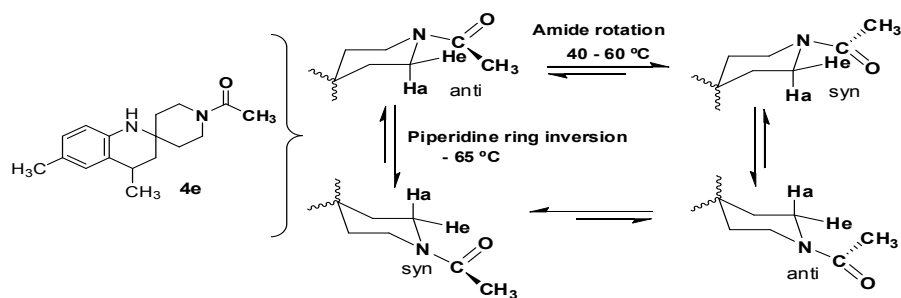
GC-MS technique to find possible products **3A**, **3B** and **4** that could be formed during this process (Scheme 4).

Detailed GC-MS analysis followed by ¹H NMR experiments of all series of each purified amide showed the following results: 1. reaction of formamide and acetamide spiro derivatives **3** did perform fully toward N-acylpiperidine products **4** without observation of any other products: nor **3A**, neither **3B**; 2. crude reaction mixture of debenzoylation reaction for the benzamide series contained a small amount (<10% by GC-MS) of products **3A**. Many attempts to improve the benzoyl migration process have failed. (Major loading of reactants or long time reaction did not improve situation). These findings gave us a basis to believe in a possible intramolecular acyl transfer reaction during the debenzoylation process induced by HCOONH₄. To prove this fact we resorted to a crossover experiment technique that is particularly relevant for many molecular rearrangements [33]. Three types of similar experiments were carried out: a) with mixture of two different acetamides **3a** and **3e** (Exp. 1); b) with mixture of acetamide **3b** and formamide **3k** (Exp. 2), and c) with mixture of acetamide **3b** and formamide **3i** (Exp. 3) (Scheme 5).

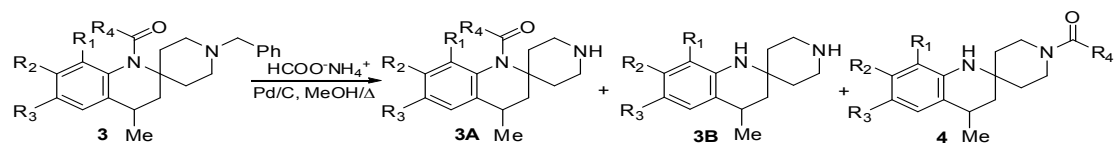
These amides mixtures were subjected to the same reaction conditions, in which each rearranged N-acylpiperidine products were obtained. GC-MS analysis of the final product's crude reaction revealed that each mixture produced only the corresponding N-acylpiperidine derivatives **4** that were obtained during the independent experiments. Although these experiments were a good evidence for intramolecular acyl transfer reactions, it was decided to find another proof for a workable hypothesis, the trapping technique. Piperidine and morpholine molecules were chosen, because they are more suitable nitrogen reactants with similar nucleophilic characteristics. Thus, an equimolar mixture of acetyl derivative **3e** and piperidine (morpholine) was subjected to a debenzoylation reaction keeping the same reaction conditions. The GC-MS data of final product's crude reaction indicated the formation of compound **4e** and did not show any formation of N-acetylpiperidine or N-acetylmorpholine (Scheme 6).

With this information, it was concluded that studied acyl transfer reactions in spiro-piperidine series are intramolecular. Based on the findings, we could propose a plausible mechanism given in Scheme 7 that explains a remarkable reactivity of compound **3**.

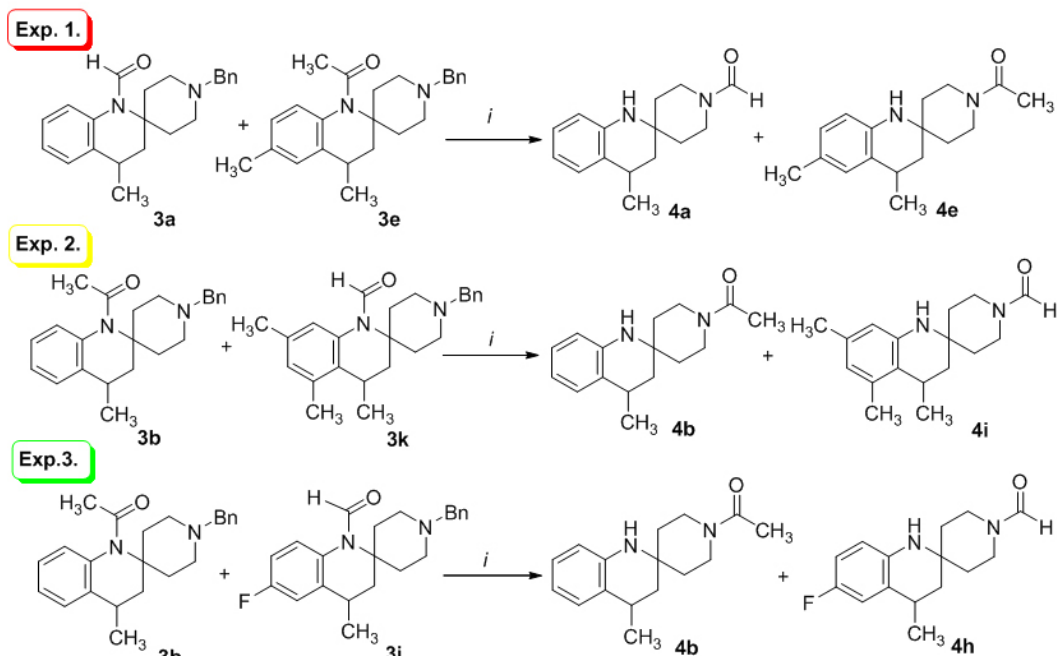
After careful examination of the synthetic results it has been concluded that according to the migration capacity, acyl groups are arranged in the following order: acetyl > formyl > phenyl, based on the tetrahedral mechanism [34]. This mechanism suggests an initial attack of a



Scheme 3. Conformational equilibrium for acetamide **4e**.

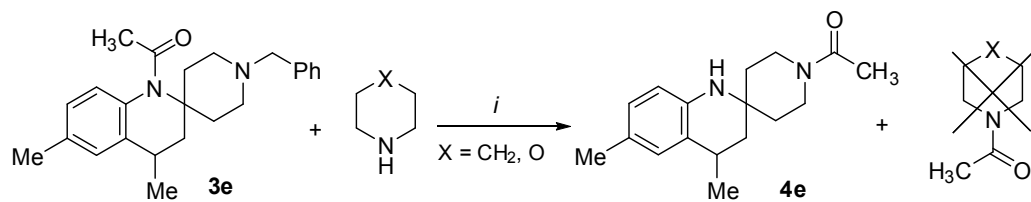


Scheme 4. Possible products of debenzylation process.



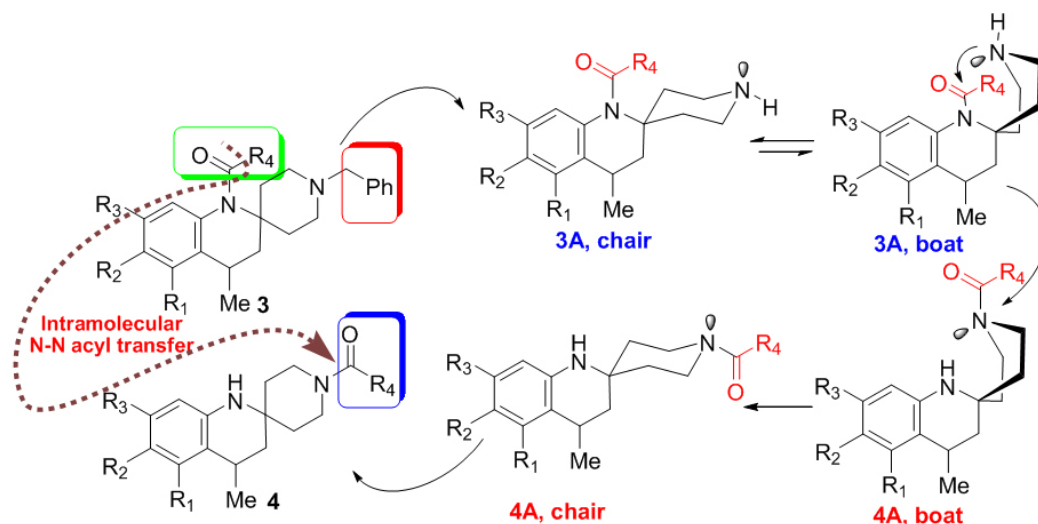
i. acyl amides **3** (1 mmol), $\text{HCOO}^-\text{NH}_4^+$ (5 mmol), Pd/C (2.5% mmol), MeOH (10 mL), $T = 64^\circ\text{C}$, $t = 10$ min.

Scheme 5. Crossover experiments of two different amides.



i. **3e** (1 mmol), piperidine or morpholine (1 mmol), $\text{HCOO}^-\text{NH}_4^+$ (5 mmol), Pd/C (2.5% mmol), MeOH (10 mL), $T = 64^\circ\text{C}$, $t = 10$ min.

Scheme 6. Acetyl trapping experiments with piperidine (morpholine) molecules.



Scheme 7. Intramolecular acyl transfer reaction in spiro piperidine system **4**.

nucleophile on a carbonyl group that could result in joining to the carbonyl group followed by elimination of the leaving group. Thus, the migratory aptitudes of these acyl groups would depend on a combination of the inductive effect of the radical on the reactivity of the C=O group and on the ease of expelling the leaving group by the tetrahedral intermediate.

4. Conclusions

In summary, we described an efficient and useful synthesis of new and attractive spiro piperidine scaffolds based on an intramolecular acyl transfer process using simple and mild debenzoylation reaction conditions. Through rigorous examination of all spectroscopic information it was possible to correctly assign amide configurations and piperidine ring conformations that are closely involved in the acyl migration reaction. Among

these acyl transfer reactions, acetyl migration was chosen to be the best; it is easy to perform, clean, fast, efficient, economic and possible under green reaction conditions. Detailed spectroscopic data analysis would certainly be very useful in piperidine alkaloid chemistry and in drug design and development. Biological assays of spiro piperidine products obtained in this investigation and further applications of this methodology to similar piperidine systems will be disclosed in due course.

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