ONE-POT SYNTHESIS OF SPIRO-3,4-DIHYDRO-2H-PYRROLES THROUGH TANDEM NUCLEOPHILIC CYCLISATION REACTION

Nandkishor Chandan

Department of Chemistry, Siddharth College of Arts, Science and Commerce,
Fort Mumbai-400 001, Maharashtra, INDIA.

✉Corresponding Author: nandkishorc@gmail.com

ABSTRACT

A very simple and convenient one-pot synthesis of Spiro-3,4-dihydro-2H-pyrrole has been developed while synthesizing 2,2,5-trisubstituted pyrrolidines. Initially, the Meldrum's acid was treated with α,β -unsaturated ketones in presence of anhydrous carbonate base and phase transfer catalyst benzyltriethylammonium chloride in acetonitrile as a solvent to afford the Michael adduct which was readily converted to the corresponding oxime using standard conditions. The crude oxime was treated directly with *p*-toluenesulfonyl chloride to tosylate the oxime but instead in presence of an excess of organic base as Et_3N results in tandem nucleophilic cyclization to spirobicyclic compound as Spiro-3,4-dihydro-2H-pyrrole as product directly, instead of the tosyloxime. So, it was considered to be a novel route to synthesized spirocyclic compounds as it is the skeleton of many natural products and pharmaceutical products.

Keywords: Pyrrole, Spiro, Oxime, Tosyloxime, Cyclization, Meldrum's Acid, Tandem, Nucleophilic, α,β -Unsaturated Ketone.

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INTRODUCTION

The substituted Pyrroles are the most important and explored heterocyclic compounds as they are found in many natural products and biologically active compounds¹⁻³ as well are privileged scaffolds for pharmaceutical products⁴⁻⁸ since they exhibit a diverse range of biological activities, including analgesic, anti-convulsant, anti-depressant, anti-allergic, anti-diabetic, anti-hyperlipidemic, anti-microbial, anti-fungal, anti-viral, anti-inflammatory, cholesterol-reducing, and anti-tumor properties.⁹⁻¹² Therefore, substituted pyrroles are considered as a potential source of biologically active compounds with valuable properties.

The Spiro heterocyclic compounds are considered as a privileged framework because of their rigidity, three-dimensional geometries, and wide distribution in various natural products and synthetic molecules. Presently, the Spiro-heterobicyclic compounds are attracting considerable interest in synthetic organic chemistry because of their molecular structure and diverse biological activities¹³. In addition, spiro-heterocycle systems impart structural novelty for drug discovery because of its broad range of medicinal properties,¹⁴⁻¹⁸ as well important structural motifs that are entrenched in a variety of drugs, including the cardiovascular active Irbesartan,¹⁹⁻²⁰ progestogenic agent Drospirenone²¹⁻²² and potassium-separating diuretic Spironolactone.²³⁻²⁴ The normally used approach in drug designing is to rigidify the ligand conformation by a spiro-ring fusion, which can impact ligand binding entropy upon binding to a protein target. Commonly, bioactive spirocyclic molecules have five-membered ring systems in their structures. In particular, spiro-pyrroles represent important structural motifs that can be found in many biologically active synthetic compounds and natural products.²⁵⁻²⁶ We have recently reported that, under basic conditions, tosyloxime of Michael adduct with diethyl malonate results in the cyclization with C-N bond formation to pyrrolidine embedded with various functionality²⁷⁻²⁸. In a similar line to introduced the rigidity, we have used Meldrum's acid as a source of nucleophile in Michael addition reaction with different α,β -unsaturated ketones which on oximation and followed by tosylation more than basic condition results into the Spiro-3,4-dihydro-2H-pyrrole in good yield as one-pot synthesis (Fig.-1).

Fig.-1: Cyclization Leads to Spiro Compound

EXPERIMENTAL

General Procedure for the Preparation of Michael Adduct⁹⁻¹²

To a stirring solution, 7.63 mmol of Meldrumic acid (1.1g) in acetonitrile (20 ml) was added 8.39 mmol of anhydrous K_2CO_3 (1.15g) and 7.63 mmol of benzyltriethylammonium chloride (1.73g). The mixture was stirred for 15 min at rt and 7.63 mmol of methyl vinyl ketone (0.64ml) was then added and the resultant mixture was stirred for 8 hr at 50°C. After TLC was monitored, the mixture was cooled to rt and the reaction was quenched with water and mixture was washed with diethyl ether, then acidified by 6 N HCl. The adduct was extracted by diethyl ether and dried over Na_2SO_4 , to give the crude product, which was purified by recrystallization using EtOAc and petroleum ether to afford Michael adduct **1**.

General Procedure for the Preparation Oxime of Michael Adduct²⁷⁻²⁸

To the solution of 2.33 mmol Michael adduct ketone **1** (500mg) in 10 ml EtOH was added 4.66 mmol of $NH_2OH \cdot HCl$ (183mg) and 4.66 mmol of Et_3N (470mg) and the reaction mixture was heated to 50°C for 1 hr. The progress of the reaction was monitored by TLC and on completion of the reaction mixture was allowed to cool to room temperature. EtOH was removed under reduced pressure and the residue was dissolved in EtOAc and H_2O added. The organic layer was separated, washed with brine and dried over Na_2SO_4 . The concentration of the organic layer gave the crude product, which was purified by flash column chromatography (eluting with EtOAc : petrol) to afford the oxime product **2**.

General Procedure for Cyclization to Spiro-3,4-dihydro-2H-pyrrole²⁹

The stirring solution 2.18 mmol of **2** oxime (500mg) in dry 10 ml CH_2Cl_2 at 0 °C was treated with 6.54 mmol of Et_3N or pyridine (660mg or 516mg) followed by slow addition of 2.61 mmol of *p*-toluenesulphonyl chloride (494mg) and the reaction was stirred for 1 hrs and it was found in mass spectra showed the presence of the cyclized product. The reaction mixture was further stirred for 2 hrs and the reaction progress was monitored by TLC and by mass spectra and it was found that instead of tosyloxime the cyclized product was formed and after completion of the reaction (1 M) HCl was added and the product was extracted by CH_2Cl_2 and the extracts were washed with saturated $NaHCO_3$ and dried over Na_2SO_4 . The concentration of CH_2Cl_2 gave the crude product which was purified by flash column chromatography (eluting with EtOAc : petrol) to afford the Spiro-3,4-dihydro-2H-pyrrole.

(±) Dimethyl-5-(3-oxobutyl)-1,3-dioxane-4,6-dione, **1**³²

Following the general procedure **1**, to the stirring solution 15.3 mmol of Meldrumic acid (2.21g) in acetonitrile (40 ml) was added 16.8 mmol of anhydrous K_2CO_3 (2.31g) and 15.3 mmol of benzyltriethylammonium chloride (3.48g). The mixture was stirred for 15 min at rt and 15.3 mmol of methyl vinyl ketone (1.3ml) was then added and the resultant mixture was stirred for 8 hr at 50 °C to give crude product, which was purified by recrystallization using EtOAc and petroleum ether to afford adduct **1** (2.67 g, 81%) as pale yellow solid (m.p. = 116-118 °C, *lit* 119-120 °C)⁹⁹; R_f = 0.16 (EtOAc : petrol, 1:1); ν_{max} (film)/ cm^{-1} 2892, 1785, 1747, 1710, 1382, 1303, 1249, 1165, 1010, 986, 730; δ_H (400 MHz; $CDCl_3$; Me_4Si) 1.74, 1.78 (6H, s, $C(CH_3)_2$), 2.13 (3H, s, $COCH_3$), 2.78 (2H, m, CH_2CH_2CH), 2.75 (2H, t, J 7.1 Hz, CH_2CH_2CH), 3.86 (1H, t, J 5.4 Hz, CH_2CH_2CH); δ_C (100 MHz; $CDCl_3$; Me_4Si) 19.5 (CH_2CH_2CH), 25.8, 27.9 $C(CH_3)_2$, 29.5 ($COCH_3$), 38.7 (CH_2CH_2CH), 44.0 (CH_2CH_2CH), 104.5 ($C(CH_3)_2$), 164.7 (2 x COO), 207.5 (CO); m/z (ESI⁺) 213, ($[M-H]^+$, 100%), HRMS (ESI⁺) $C_{10}H_{13}O_5^-$ ($[M-H]^+$) requires 213.0768; found 213.0762.

(±) 5-(3-(Hydroxyimino)butyl)-2,2-dimethyl-1,3-dioxane-4,6-dione, 2²⁷⁻²⁸

Following the general procedure **2**, to the solution 6.44 mmol of Michael adduct **1** (1.38 g) in EtOH (30ml), 12.88 mmol of NH₂OH.HCl (888mg) and 12.88 mmol of Et₃N (1.30g) was added and the mixture was gently heated (50 °C) for 1 hrs, to give crude product which was purified by flash column chromatography to afford oxime **2** (1.14 g, 77%) as pale yellow semi-solid; *R_f* = 0.23 (EtOAc : petrol, 1:1); *v*_{max}(film)/cm⁻¹ 3319, 2982, 1786, 1743, 1715, 1372, 1307, 1240, 1176, 1012, 982, 731; (major isomer) δ_{H} (400 MHz; CDCl₃; Me₄Si) 1.74, 1.78 (6H, s, C(CH₃)₂), 1.94, 1.91 (3H, s, CNOHCH₃), 2.31 (2H, m, CH₂CH₂CH), 2.44, 2.63 (2H, t, *J* 7.4 Hz, CH₂CH₂CH), 3.68 (1H, t, *J* 6.8 Hz, CH₂CH₂CH), 9.33 (1H, bs, OH); δ_{C} (100 MHz; CDCl₃; Me₄Si) 13.9, 15.1 (CNOHCH₃), 21.3, 22.1 (CH₂CH₂CH), 26.2, 27.3 (C(CH₃)₂), 32.2, 35.9 (CH₂CH₂CH), 44.8 (CH₂CH₂CH), 104.8, 106.1 (C(CH₃)₂), 157.6, 158.1 (C=NOH), 162.7, 164.9 (2 x COO); *m/z* (ESI⁻) 228 ([M-H]⁻, 100%), HRMS (ESI⁻) C₁₀H₁₄NO₅⁻ ([M-H]⁻) requires 228.0881; found 228.0877.

(±) 2,8,8-Trimethyl-7,9-dioxa-1-azaspiro[4.5]dec-1-ene-6,10-dione, 3³⁴⁻³⁵

Following the general procedure **3**, to the solution 1.79 mmol of oxime **2** (412mg) in dry CH₂Cl₂ (20ml) was added 5.37 mmol of Et₃N (542mg) at 0°C and followed by 2.15 mol of *p*-toluenesulphonyl chloride (410 mg) and the mixture stirred for 30 min instead tosyl oxime, isolated cyclized product as spirobicyclic pyrrolidine which was purified by flash column chromatography to afford compound **3** (297 mg, 78%) as a crystalline solid; m.p. = 98 °C; *R_f* = 0.63 (EtOAc : petrol, 1:1); *v*_{max}(film)/cm⁻¹ 2933, 1782, 1731, 1452, 1170, 914, 731; δ_{H} (400 MHz; CDCl₃; Me₄Si) 1.78, 2.06 (C(CH₃)₂), 2.16 (3H, s, N=CCH₃), 2.59 (2H, t, *J* 7.6 Hz, C(4)HH), 2.97 (2H, t, *J* 7.6 Hz, C(3)HH); δ_{C} (100 MHz; CDCl₃; Me₄Si) 19.2 (COCH₃), 28.3, 28.5 C(CH₃)₂, 31.4 (C4), 41.2 (C3), 80.7 (C2), 106.2 C(CH₃)₂, 167.4 (2 x COO), 182.9 (C5); *m/z* (ESI⁺) 445 ([2M+Na]⁺, 100%), 234 ([M+Na]⁺, 95%), HRMS (ESI⁺) C₁₀H₁₃NNaO₅⁺ ([M+Na]⁺) requires 234.0742; found 234.0737.

(±) 4,8,8-trimethyl-2-phenyl-7,9-dioxa-1-azaspiro[4.5]dec-1-ene-6,10-dione, 6

Following the general procedure **3**, to the solution 0.95 mmol of oxime **5** (289 mg) in dry CH₂Cl₂ (15 ml) was added 2.85 mmol of Et₃N (288mg) at 0°C and followed by 1.14 mmol of *p*-toluenesulphonyl chloride (216 mg) and the mixture was stirred for 30 min instead tosyl oxime, isolated cyclized product as spirobicyclic pyrrolidine which was purified by flash column chromatography to afford compound **6** (160 mg, 59%) as a crystalline solid; m.p. = 103 °C; *R_f* = 0.46 (EtOAc : petrol, 1:1.5); *v*_{max}(film)/cm⁻¹ 3078, 2956, 1779, 1737, 1170, 912, 740; δ_{H} (400 MHz; CDCl₃; Me₄Si) 0.96 (3H, d, CH₃), 1.75, 2.00 (C(CH₃)₂), 2.55 (2H, d, *J* 7.5 Hz, C(4)HH), 2.79 (1H, m, C(3)H), 7.3-7.9 (ArH); δ_{C} (100 MHz; CDCl₃; Me₄Si) 28.9, 28.2 C(CH₃)₂, 31.9 (C4), 41.0 (C3), 89.7 (C5), 106.0 C(CH₃)₂, 112-139 (ArC), 167.0 (2 x COO), 180.9 (C2); *m/z* (ESI⁺) 310 ([M+Na]⁺, 95%), HRMS (ESI⁺) C₁₆H₁₇NNaO₄⁺ ([M+Na]⁺) requires 310.1055; found 234.1076.

(±) 8,8-dimethyl-2-phenyl-7,9-dioxa-1-azaspiro[4.5]dec-1-ene-6,10-dione, 9

Following the general procedure **3**, to the solution 0.69 mmol of oxime **8** (200mg) in dry CH₂Cl₂ (10ml) was added 2.07 mmol of Et₃N (209mg) at 0°C and followed by 0.83 mmol of *p*-toluenesulphonyl chloride (157 mg) and mixture was stirred for 30 min instead tosyl oxime, isolated cyclized product as spirobicyclic pyrrolidine which was purified by flash column chromatography to afford compound **9** (120 mg, 64%) as a crystalline solid; m.p. = 97 °C; *R_f* = 0.53 (EtOAc : petrol, 1:1); *v*_{max}(film)/cm⁻¹ 3093, 2931, 1778, 1735, 1177, 910; δ_{H} (400 MHz; CDCl₃; Me₄Si) 1.70, 2.03 (C(CH₃)₂), 2.52 (2H, t, *J* 7.4 Hz, C(4)HH), 2.90 (2H, t, *J* 7.4 Hz, C(3)HH), 7.3-7.9 (ArH); δ_{C} (100 MHz; CDCl₃; Me₄Si) 28.9, 28.2 C(CH₃)₂, 31.9 (C4), 41.0 (C3), 89.7 (C5), 106.0 C(CH₃)₂, 114-138 (ArC), 167.0 (2 x COO), 180.9 (C2); *m/z* (ESI⁺) 296 ([M+Na]⁺, 95%), HRMS (ESI⁺) C₁₅H₁₅NNaO₄⁺ ([M+Na]⁺) requires 296.0899; found 234.0901.

(±) 2,4,8,8-tetramethyl-7,9-dioxa-1-azaspiro[4.5]dec-1-ene-6,10-dione, 12

Following the general procedure **3**, to the solution 0.88 mmol of oxime **11** (215mg) in dry CH₂Cl₂ (10ml) was added 2.64 mmol of Et₃N (267mg) at 0°C and followed by 1.06 mmol of *p*-toluenesulphonyl

chloride (201 mg,) and the mixture stirred for 30 min instead tosyl oxime, isolated cyclized product as spirobicyclic pyrrolidine which was purified by flash column chromatography to afford compound **12** (111 mg, 56%) as a crystalline solid; m.p. = 99 °C; R_f = 0.51 (EtOAc : petrol, 1:1); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2934, 1780, 1732, 1456, 1172, 915, 735; $\delta_{\text{H}}(400 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 0.98 (3H, d, CH_3), 1.79, 2.05 ($\text{C}(\text{CH}_3)_2$), 2.16 (3H, s, $\text{N}=\text{CCH}_3$), 2.64 (1H, m, $\text{C}(4)\text{H}$), 2.94 (2H, d, J 7.5 Hz, $\text{C}(3)\text{HH}$); $\delta_{\text{C}}(100 \text{ MHz}; \text{CDCl}_3; \text{Me}_4\text{Si})$ 18.2, (CH_3), 21.5 ($\text{N}=\text{CCH}_3$), 28.4, 28.7 ($\text{C}(\text{CH}_3)_2$), 32.1 ($\text{C}(4)$), 43.2 ($\text{C}(3)$), 88.9 ($\text{C}(5)$), 106.7 ($\text{C}(\text{CH}_3)_2$), 167.9 (2 x COO), 182.8 ($\text{C}(2)$); m/z (ESI^+) 248 ($[\text{M}+\text{Na}]^+$, 95%), HRMS (ESI^+) $\text{C}_{11}\text{H}_{15}\text{NNaO}_4^+$ ($[\text{M}+\text{Na}]^+$) requires 248.0899; found 234.0839.

The instruments used for the data analysis are NMR instruments with models are AVG400/AVF400/AVB400 and IR-Spectrometer used FTS6000/FTS7000 and for mass spectra we used LC-MS LCT

RESULTS AND DISCUSSION

Spiro-heterobicycles appear in countless natural products and clinically valuable compounds²⁹ possibly among the most challenging structural motifs to synthesize, spirocyclic synthesis has inspired chemists for decades. Meldrum's acid appears to be an attractive reagent in organic synthesis owing to its high acidity, steric rigidity and high reactivity.³⁰ Following the methodology developed²⁷ using oxime ether mediated ring closure, Meldrum's acid could be very useful to synthesize spiro-heterobicyclic rings. Indeed, the spiro-heterobicyclic compound **3** could be helpful to construct non-natural amino acid by solvolysis of Meldrum's acid with alcohols would give a diastereomeric mixture of a half acid ester; and there could be further interconverted. The half carboxylic acid can be converted into amine or carbamate, through acid azide formation and followed by Curtius rearrangement would give an isocyanate, which could be easily converted into amine or carbamate by hydrolysis or alcohol treatment.³¹

The required spiro-heterobicyclic compound **3** could be synthesized by following the sequence of reactions. The reaction of Meldrum's acid with methyl vinyl ketone in presence of 1.1 eq. of anhydrous K_2CO_3 and 1 eq. of benzyltriethylammonium chloride in acetonitrile as the solvent, at 50-60 °C for 8-10 hr³² afforded the Michael adduct **1** in 81% yield with some double Michael addition product as a by-product which was minimized by using 1.1eq. base. The Michael adduct **1** was readily converted to the corresponding oxime using standard conditions ($\text{NH}_2\text{OH} \cdot \text{HCl}$ and Et_3N in EtOH stirred at 50°C for 1 hr) and afforded **2** in 77% yield. The crude oxime **2** was used directly and treatment with *p*-toluenesulfonyl chloride and base (excess Et_3N in dry CH_2Cl_2 at rt) gave the cyclized product as Spiro-3,4-dihydro-2H-pyrrole **3** directly in 78% of yield (Scheme-1) instead of the expected tosyl oxime (Scheme-1).

Reagent and Conditions: (a) Anhydrous K_2CO_3 benzyltriethylammonium chloride, acetonitrile heated 50-60°C; (b) $\text{NH}_2\text{OH} \cdot \text{HCl}$, Et_3N , EtOH , heated 50°C; (c) $p\text{TsCl}$, Et_3N , CH_2Cl_2 , rt.

Scheme-1: Synthesis of Spiro Compound

The resultant Spiro-3,4-dihydro-2H-pyrrole **3** is crystalline and this product was fully characterized by single-crystal X-ray crystallographic analysis (Fig.-2), clearly demonstrating the fully orthogonal nature of the two heterocyclic rings. The spiro-heterobicyclic compound **3** was previously reported by Danheiser³³ and he obtained it as oil but NMR data agree.

Fig.-2: X-ray Crystal Structure for Spiro-3,4-dihydro-2H-pyrrole **3**

Similarly, the Michael addition reaction with Meldrum's acid and α,β -unsaturated ketones such as 1-phenylbut-2-en-1-one, 1-phenylprop-2-en-1-one, pent-3-en-2-one and chalcone were carried out in presence of anhydrous K_2CO_3 and 1 eq. of benzyltriethylammonium chloride in acetonitrile as the solvent, at 50-60 °C for 8-10 hr except chalcone other ketone gave good yield as Michael adduct as shown in scheme 2. The same Michael adduct on oximation using standard condition and followed by treatment with *p*-toluenesulfonyl chloride and base (excess Et_3N in dry CH_2Cl_2 at rt) gave the cyclization product Spiro-3,4-dihydro-2H-pyrrole as **6**, **9** and **12** in good yield as shown in Scheme-2 but as the compounds are solid but the formation of single crystal was so difficult and all compounds are characterized by Mass and NMR spectroscopy. The same click chemistry was not possible with chalcone may be due to high steric factor.

Reagent and conditions: (a) Anhydrous K_2CO_3 benzyltriethylammonium chloride, acetonitrile heated 50-60°C; (b) $NH_2OH.HCl$, Et_3N , $EtOH$, heated 50°C; (c) $pTsCl$, Et_3N , CH_2Cl_2 , rt.

Scheme-2: Synthesis of Substituted Spiro Compounds³⁶

CONCLUSION

In summary, we have developed a one-pot methodology for the synthesis of spiro-heterobicyclic compounds as Spiro-3,4-dihydro-2H-pyrroles with alkyl and aryl substitutions on the five-member heterocycle. It was also concluded that both aryl groups as substitution were not possible as we have started with chalcone as starting material and reaction did not work. The method is useful to synthesize the rigid spiro-heterocycle which can also be converted to the non-natural amino acids by hydrolysis to half acid ester and interconvert to amino group through Curtius rearrangement reaction. This methodology developed will be very useful to get quick access to synthesize Spiro-3,4-dihydro-2H-pyrroles which is a part of many natural products of high importance.

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