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A Synthetic Route Towards 3, 4-disubstituted Pyrrolidin-2-ones via Michael Addition and Reductive Ring Closing Strategy

Monali Dawange[a], Nikita Parekh[a], Avinash Kumbhar[a], Wim Dehaen[b] and Radhika Kusurkar*[a]

[a]Department of Chemistry, S P Pune University, Pune 411007, India

[b]Molecular Design and Synthesis, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, 3001 Leuven, Belgium

Pyrrolidin-2-one derivatives were synthesized via DABCO mediated Michael addition of isoxazol-5(4*H*)-ones with nitroalkenes, followed by one pot reduction of nitro group and ring cleavage with cyclization. 2-Pyrrolidinone scaffolds with a wide range of substitution were synthesized with good yield and diastereoselectivity by using this protocol.

INTRODUCTION

Nitrogen containing heterocycles are the most common scaffolds present in bioactive materials as well as pharmaceuticals.[1] 2-Pyrrolidinone, a class of 5-membered lactam has always been attractive synthetic target due to its occurrence in biological as well as pharmaceutical compounds. Some of the naturally occurring compounds containing 2-pyrrolidinones are epolactaene (**1**) having anticancer activity[2] and rigidiusculamide A (**2**) exhibiting cytotoxicity[3] against human tumor cell lines HeLa and MCF-7 (Figure 1).

A number of pharmaceutically active drugs include 2-pyrrolidinone core e.g. rolipram (**3**) as antidepressant[4] and levetiracetam (**4**) a member of Racetam class drugs, as an antiepileptic drug[5] (Figure 1). Owing to their importance, many methods have been reported[6] for the synthesis of substituted 2-pyrrolidinones.

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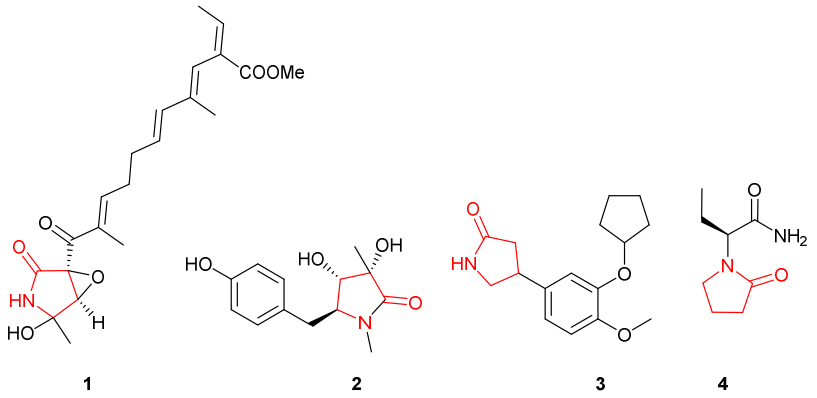
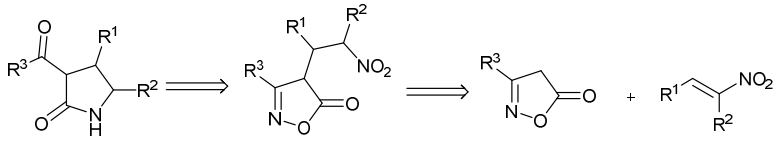


Figure 1. Naturally occurring and synthetic drug molecules containing 2-pyrrolidinone unit

Isoxazol-5(4*H*)-ones have always been versatile substrates in synthetic organic chemistry. A large number of reactions are reported in the literature on the reactivity of isoxazol-5(4*H*)-ones such as Michael addition,[7] aza-Michael addition,[8] Pd-catalysed C-alkylation,[9] nucleophilic ring opening,[10] Vilsmeier-Haack reaction,[11] flash vacuum pyrolysis,[12] condensation reactions,[13] and organocatalytic asymmetric fluorination.[14] Nevertheless, only one report[14b] is available on the Michael addition of isoxazol-5(4*H*)-ones with *β*-nitroalkenes. The Michael adduct can be further transformed to different scaffolds however it is not much explored.

The Michael addition reaction is one of the important C-C bond forming reaction. Michael addition of pyrazolones with nitroalkenes followed by reductive cyclization for the synthesis of pyridine fused pyrazolones have been reported by us recently.[15] Herein, we describe the Michael addition of isoxazol-5(4*H*)-one derivatives with various *β*-nitroalkenes and further reductive ring cleavage and cyclization to provide a wide range of substituted pyrrolidin-2-one derivatives (Scheme 1).



Scheme 1. Retrosynthetic strategy towards pyrrolidin-2-one derivatives

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RESULTS AND DISCUSSION

In the beginning, the starting compound 3-phenylisoxazol-5(4*H*)-one (**2a**) was prepared by reacting ethyl benzoylacetate with hydroxylamine hydrochloride in ethanol according to literature procedure.[16] We first carried out a model reaction with 3-phenylisoxazol-5(4*H*)-one (**2a**) and *trans*-*β*-nitrostyrene (**1a**) using a catalytic amount of acetic acid (20 mol%) in ethanol under reflux condition. The desired Michael adduct **3a** was isolated in 79% yield after 4 h (Table 1, entry 1). To standardize the reaction, various conditions were tried as shown in Table 1. When 1 equiv. of triethyl amine was added instead of acetic acid, the Michael adduct **3a** was isolated in 75% yield after 5 h (Table 1, entry 2). A lower yield (45%) was observed when DBU was used as a base in methylene chloride at room temperature and reaction was incomplete even after 24 h (Table 1, entry 3). When DABCO was used as a base in methylene chloride at room temperature, product **3a** was obtained in excellent yield (89%); moreover the reaction time was reduced to 30 min (Table 1, entry 4). Further, base loading was reduced to check the reaction progress, but it slowed down the reaction rate and the reaction was incomplete even after 24 h (Table 1, entry 5, 6, 7). When 1 equiv. of DMAP was tried, the reaction was still incomplete and product **3a** was isolated in 59% yield after 24 h (Table 1, entry 8). While, reaction in pyridine was quite slow as compared to other bases and furnished only 41% of **3a** after 24 h (Table 1, entry 9). In the absence of acid or base additive, no reaction was observed. Ultimately, the optimal reaction condition was found to be the use isoxazolone, nitroalkene and DABCO in methylene chloride in 1:1:1 molar ratio at room temperature.

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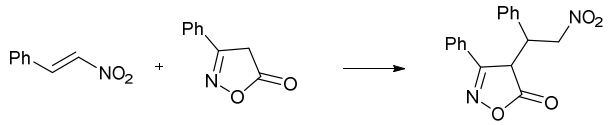
Table 1. Optimization of the Michael addition reaction[a]



1a 2a 3a

entry	condition[a]	equiv	time (h)	Yield (%)[b]
1	AcOH, EtOH, reflux	20 mol%	4	79
2	Et_3N, EtOH, reflux	1	5	75
3	DBU, DCM, rt	1	24	45 (incomplete)
4	**DABCO, DCM, rt**	**1**	**0.5**	**89**
5	DABCO, DCM, rt	0.1	12	55 (incomplete)
6	DABCO, DCM, rt	0.2	24	57 (incomplete)
7.	DABCO, DCM, rt	0.5	24	63 (incomplete)
8.	DMAP	1	24	59 (incomplete)
9.	Pyridene	1	24	41 (incomplete)
10.	DCM, rt	-	12	No reaction

[a]Reaction condition : **1a** (1.24 mmol) and **2a** (1.24 mmol) were stirred. [b]Isolated yield.

Under the optimized conditions (Table 1, entry 4), the substrate scope of substituted nitroalkenes **1a-1k** and isoxazolones **2a**, **2b**, **2c** was examined and the results are summarized in Table 2. The reaction was well tolerated with aromatic, heteroaromatic as well as aliphatic nitroalkenes. It was observed that the rate of reaction was affected by the electronic as well as steric effects. When **1d** was used for the Michael addition (Table 2, entry 4), low yields were obtained due to less reactivity of aliphatic nitroalkenes as compared to the aromatic ones. Steric hindrance affected yields of the Michael addition reaction due to the bulky nature of R^1 substituents in **1i** and **1k** (Table 2, entries 9 and 15) which resulted in reduced yield of the

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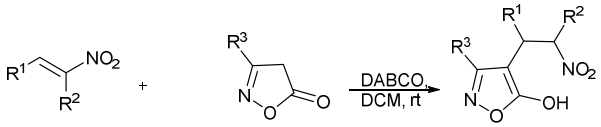
Table 2. DABCO-mediated Michael addition of nitroalkenes **1a-k** and isoxazolones **2a**, **b, c**[a]



1a; R^1 = Ph, R^2 = H
1b; R^1 = *p*-OMe-C_6H_4, R^2 = H
1c; R^1 = 2-thienyl, R^2 = H
1d; R^1 = *n*-Pr, R^2 = H
1e; R^1 = Ph, R^2 = Me
1f; R^1 = *p*-CO_2-Me-C_6H_4, R^2 = H
1g; R^1 = benzodioxole, R^2 = H
1h; R^1 = *p*-Cl-C_6H_4, R^2 = H
1i;; R^1 = cyclohexyl, R^2 = H
1j; R^1 = napthyl, R^2 = H
1k; R^1 = R^2 = 1,2-dihydronaptho

2a; R^3 = Ph
2b; R^3 = Me
2c; R^3 = *p*-Cl-C_6H_4

3a-3o

Entry	Nitroalkene	Isoxazolone	Time (h)	Product	Yield (%)[b]
1	**1a**	**2a**	0.5	**3a**	89
2	**1b**	**2a**	4	**3b**	85
3	**1c**	**2a**	1	**3c**	87
4	**1d**	**2a**	24	**3d**	53
5	**1e**	**2a**	3	**3e**	80
6	**1f**	**2a**	3	**3f**	77
7	**1g**	**2a**	4	**3g**	82
8	**1h**	**2a**	4	**3h**	62
9	**1i**	**2a**	24	**3i**	45
10	**1j**	**2a**	12	**3j**	59
11	**1a**	**2b**	3	**3k**	77
12	**1b**	**2b**	3	**3l**	73
13	**1c**	**2b**	1	**3m**	81
14	**1a**	**2c**	0.5	**3n**	79
15	**1k**	**2a**	24	**3o**	77

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[a]Reaction condition : **1** (1.24 mmol) and **2** (1.24 mmol) were stirred in presence of DABCO (1.24 mmol) in dry DCM at rt. [b]Isolated yield.

Michael adducts. All other nitroalkenes furnished a good yield of the Michael adducts. To check the substituent effect on phenyl ring (R^3) on the Michael addition, isoxazolones **2c** with 4-chloro substituent was reacted with **1a**. But changing the substituent, did not affect the rate of reaction. It was completed within 30 min and the Michael adduct **3n** was formed in 79% yield (Table 2, entry 14). Thus, it is clear that rate only depends on the nature of R^1 and R^2 substituents on the nitroalkene **1**.

In case of Michael adducts **3i**, **3k-m, 3o** products were in only one tautomeric form as seen from the ^{1}H NMR spectra. This can be attributed to the steric effect[17] of the substituents R^1 and R^3. Some of the Michael adducts showed the presence of mixture of tautomers. In those cases, DABCO was added in the ^{1}H NMR sample which suppressed one of the tautomers from the mixture. The spectra of the Michael adducts were much simplified which showed presence of only three aliphatic protons of the nitro alkyl chain similar to structure **B** or **C** respectively (Figure 2). It has been well reported[18] in literature that substituted isoxazolones can exist in three different tautomeric forms as CH (**A**), NH (**B**), or OH (**C**) form (Figure 2). The CH form is more prominent in $CDCl_3$ while only NH form is present in DMSO. In the presence of base, the OH form is noticeable in solution.

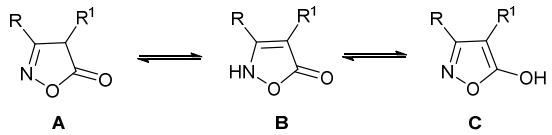

Figure 2. Possible tautomeric forms of isoxazol-5(4*H*)-one

From the analogy with the above report the Michael adducts except **3i**, **3k-m**, **3o** might be present in OH tautomeric form in DABCO. In case of adducts **3i**, **3k-m**, **3o** only the OH tautomer was seen in the ^{1}H NMR spectra without addition of DABCO.

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Having the Michael adducts in hand we proceeded further for the reduction. It is well known that Zn in acetic acid is used for the ring cleavage[19] as well as to reduce the nitro group effectively.[20] By using one pot reductive cyclization strategy with Zn/AcOH, the nitro group in the Michael adduct could be reduced to an amino and then in-situ cleavage of isoxazolone ring and cyclization would afford the desired 2-pyrrolidone core. Thus, Michael adduct **3a** was subjected to reduction at room temperature using excess of Zn in acetic acid. Within an hour, TLC analysis showed the consumption of the Michael adduct along with formation of a new compound. Assuming that the reduction of the nitro group took place initially, the reaction mixture was stirred for one hour at room temperature and further heated at 80 °C without removing Zn for 12 h. It furnished a crude product which after usual workup was found to be a mixture of two diastereomers in the ratio 99:1 from ^{1}H NMR analysis. After chromatographic purification a single diastereomer **4a** was isolated in 55% yield. In the ^{1}H NMR spectra, the product showed one downfield multiplet in the aromatic region at around 8 δ in addition to the other signals of aromatic protons, one exchangeable singlet at 6.1 δ for one proton, and four signals around 3.0 to 4.5 δ for alicyclic protons. The presence of carbonyl group in structure **4a** was supported by the signal at 195 δ in ^{13}C NMR spectrum. Finally, single crystal analysis confirmed the *trans* geometry of **4a** for the product (Figure 3; see also Supporting Information (SI) for more details).

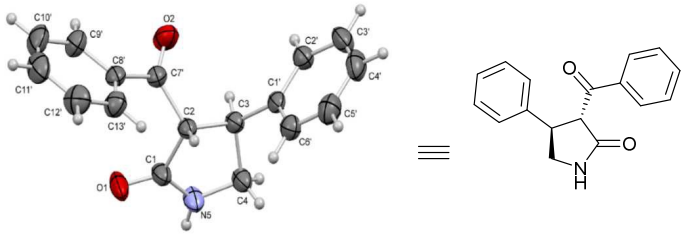

Figure 3. ORTEP diagram of **4a**

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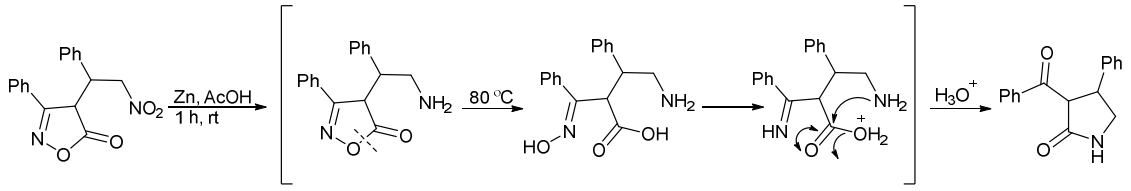
The possible mechanism for the one pot reductive cleavage is as shown in scheme 2.



Scheme 2. Plausible reaction pathway for the formation of **4a**

Further, the present protocol was applied to other Michael adducts as well. In all the cases products **4b-n** were obtained in satisfactory yield (Table 3). When Michael adduct **3e** was subjected to reductive cyclization, the crude reaction mass showed the presence of a mixture of more than two diastereomers which was confirmed from the ^{1}H NMR and was due to the presence of three stereocenters in the product. The major isomer **4e** was isolated using chromatographic separation in good yield (62%). For the confirmation of the structure of 3-acylpyrrolidin-2-ones, the crystal structure of **4l** was investigated (Figure 4; see also Supporting Information (SI) for more details) which showed the *trans* stereochemistry.

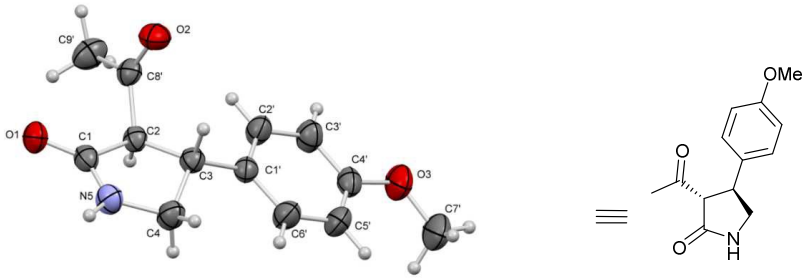


Figure 4. ORTEP diagram of **4l**

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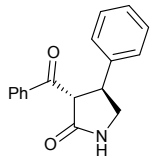
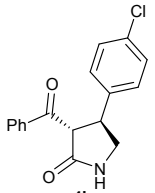
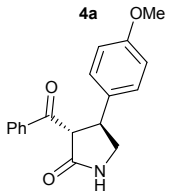
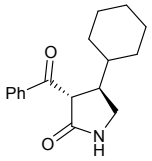
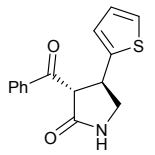
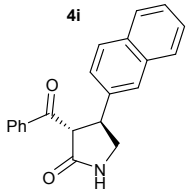
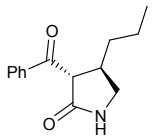
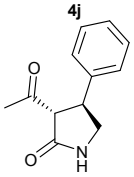
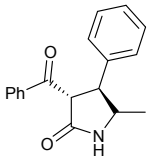
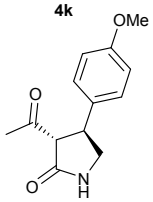
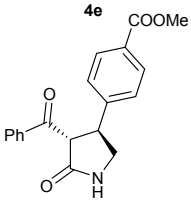
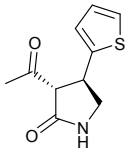
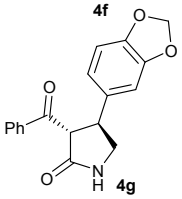
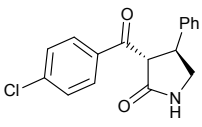
Table 3. Reductive ring cleavage followed by cyclization of Michael adducts **3a-n**[a]

entry	product[c]	yield	dr[b]	entry	product[c]	yield	dr[b]
1	 **4a**	55	>99:1	8	 **4h**	58	81:19
2	 **4b**	55	>99:1	9	 **4i**	41	>99:1
3	 **4c**	52	>99:1	10	 **4j**	44	>99:1
4	 **4d**	47	>99:1	11	 **4k**	56	>99:1
5	 **4e**	62	65:15:12:8	12	 **4l**	50	>99:1
6	 **4f**	52	94:6	13	 **4m**	47	>99:1
7	 **4g**	55	83:17	14	 **4n**	51	>99:1

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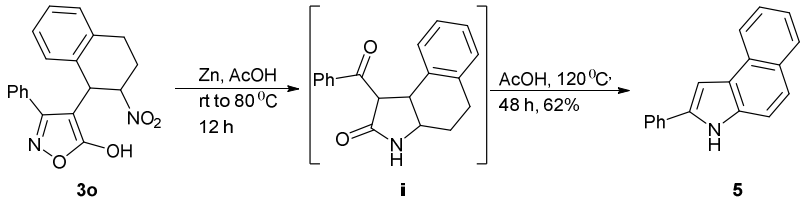
[a]Reaction condition: **3** (0.5 mmol) and Zn (5 mmol) were stirred in AcOH for 1 h at rt then heated at 80 °C for 12 h. [b]Ratios determined by ^{1}H NMR analysis of reaction mixture. [c]relative configurations of other products were assigned on the basis of analogy with **4a** and **4l**.

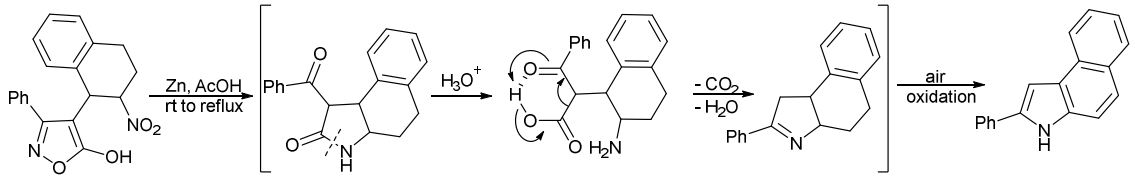
When adduct **3o** was subjected to the reaction, a complex mixture was obtained. After removal of zinc from the reaction mixture, it was further refluxed for 48 h in AcOH. The product was different than earlier products and was identified to be 2-phenyl-3*H*-benzo[*e*]indole (**5**) from spectral and analytical data (Scheme 3).



3o i 5

Scheme 3. Novel observation during reduction of adduct **3o**

Scheme 4 shows the possible mechanism for the formation of **5**.



3o i ii 5

Scheme 4. Possible mechanism for the formation of **5**

Reductive ring cleavage and cyclization resulted into the pyrrolidin-2-one (**i**), which underwent acidic hydrolysis followed by decarboxylation at high temperature resulting into the formation of cyclic imine (**ii**). Subsequent air oxidation furnished fully aromatised compound **5**. Cyclic imine formation through the amide hydrolysis and decarboxylation was well matching with the previous reports.[21] Thus, this reaction furnished a tricyclic benzo-indole scaffold.

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CONCLUSION

A novel method for the synthesis of pyrrolidin-2-one derivatives through DABCO catalysed Michael addition of isoxazol-5(4*H*)-ones and further Zn mediated one pot reductive ring cleavage followed by cyclization was achieved during the present investigation. This protocol provided a library of 2-pyrrolidinones with good yield and diastereoselectivity. Furthermore, the strategy was employed for the synthesis of a benzoindole derivative in good yield. This method opens possibility for the synthesis of a class highly substituted pyrrolidin-2-ones which can have significant utility in organic synthesis.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Michael Adducts (3a-o)

Nitroalkene **1** (1.24 mmol), isoxazolone **2** (1.24 mmol), and DABCO (1.24 mmol) were stirred in dry DCM (10 mL) under N_2 at room temperature. The progress of the reaction was monitored by TLC. When the reaction was complete, DCM was evaporated off. The crude sample was purified by column chromatography on silica gel (with petroleum ether/EtOAc as the eluent) to afford the corresponding Michael adduct **3**.

Characterization of selected compounds

4-(2-Nitro-1-phenylethyl)-3-phenyl-1,2-oxazol-5-ol ***(3a)***

^{1}H NMR (500 MHz, $CDCl_3$ with DABCO) δ 7.41-7.36 (m, 7H), 7.31-7.28 (m, 2H), 7.23-7.21(m, 1H), 5.49 (dd, J = 11.9, 10.4 Hz, 1H), 4.72 (dd, J = 12.1, 6.1 Hz, 1H), 4.49 (dd, J = 10.2, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$ with DABCO) δ 176.6, 165.2, 141.3, 132.2, 131.5, 128.8, 128.5, 128.2, 127.9, 127.1, 82.6, 78.0, 39.6; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50-7.48 (m, 3H), 7.42-7.38 (m, 4H), 7.32-7.28 (m, 2H), 7.24-7.20 (m, 1H), 6.52 (br s, 1H), 5.33 (dd, J = 12.8, 8.8 Hz, 1H), 5.11 (dd, J = 12.8, 7.3 Hz, 1H), 4.38 (t, J = 8.1 Hz, 1H); ^{13}C

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NMR (100 MHz, DMSO-d_6) δ 171.1, 162.4, 139.0, 131.3, 129.4, 129.0, 127.7, 127.5, 127.4, 126.9, 126.7, 76.3, 38.0; FT-IR (neat) 3064, 2934, 1732, 1556, 1377, 756, 698 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 311.1022, calcd for $C_{17}H_{15}N_2O_4$ 311.1026.

4-[2-Nitro-1-(thiophen-2-yl)ethyl]-3-phenyl-1,2-oxazol-5-ol ***(3c)***

^1H NMR (500 MHz, $CDCl_3$ with DABCO) δ 7.46 (dd, J = 6.5, 2.9 Hz, 2H), 7.39-7.37 (m, 3H), 7.16 (dd, J = 5.0, 1.3 Hz, 1H), 6.94-6.92 (m, 2H), 5.41 (dd, J = 11.5, 9.5 Hz, 1H), 4.86-4.77 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$ with DABCO) δ 176.3, 164.9, 144.8, 131.4, 128.8, 128.4, 128, 127.1, 124.8, 124.5, 82.6, 77.8, 34.6; FT-IR (neat) 3066, 2923, 1711, 1553, 1426, 1376, 757, 699 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 317.0593, calcd for $C_{15}H_{13}N_2O_4S$ 317.0591.

4-(1-Nitropentan-2-yl)-3-phenyl-1,2-oxazol-5-ol ***(3d)***

^1H NMR (500 MHz, $CDCl_3$ with DABCO) δ 7.51-7.49 (m, 2H), 7.44-7.39 (m, 3H), 4.98 (dd, J = 11.3, 9.8 Hz, 1H), 4.47 (dd, J = 11.4, 6.2 Hz, 1H), 3.31-3.25 (m, 1H), 1.69-1.63 (m, 1H), 1.40-1.36 (m, 1H), 1.30-1.25 (m, 1H), 1.14-1.12 (m, 1H), 0.75 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$ with DABCO) δ 176.1, 165. 8, 132.2, 129.5, 128.7, 128.5, 128.4, 78.4, 33.6, 33.6, 20.4, 13.9; FT-IR (neat) 3065, 2961, 1697,1549, 1379, 758, 696 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 277.1184, calcd for $C_{14}H_{17}N_2O_4$ 277.1183.

4-(2-Nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-phenyl-1,2-oxazol-5-ol ***(3o)***

mp 145-147 °C; ^1H NMR (400 MHz, $CDCl_3$ without DABCO) δ 7.59-7.5 (m, 5H), 7.19-7.12 (m, 3H), 6.98 (d, J = 7.4 Hz, 1H), 5.52 (td, J= 11.6, 3.5 Hz, 1H), 4.64 (d, J = 10.4 Hz, 1H), 3.16-3.09 (m, 1H), 3.03-2.99 (m, 1H), 2.58-2.55 (m, 1H), 2.40-2.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$ without DABCO) δ 170.6, 165.5, 134.9, 133.4, 132.1, 129.7, 129.0, 127.8, 127.4, 127.1, 126.5, 102.1, 84.4, 38.7, 28.7, 28.0; FT-IR (neat) 3065, 2956, 1709, 1547,

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1374, 758, 698 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 337.1184, calcd for $C_{19}H_{17}N_2O_4$ 337.1183.

General Procedure for Reductive Cyclization (4a-n and 5)

To a stirred solution of Michael adduct **3** (0.5 mmol) in acetic acid (10 mL) was added zinc dust (5 mmol). The reaction mixture was stirred for 1 h at room temperature. After disappearance of the starting material (monitored by TLC), the reaction mixture was subjected for heating at 80 °C for 24 h and then filtered through celite. The reaction mixture was evaporated under reduced pressure to remove acetic acid. The residue was quenched with water, washed with saturated $NaHCO_3$ solution and extracted with ethyl acetate, dried over sodium sulfate and concentrated. Purification was done by column chromatography using chloroform/ MeOH as the eluent.

Michael adduct **3o** (178 mg, 0.5 mmol) was reacted with Zn (0.346 mg, 5 mmol) according to the general procedure for reductive cyclization. After heating the reaction mass at 80 °C for 12 h, Zn was removed and the mixture was further refluxed in AcOH for 48 h in open air. After usual work up; the mixture was purified by column chromatography to furnish solid product **5**.

Characterization of selected compounds

*(3S,4S)-3-Benzoyl-4-phenylpyrrolidin-2-one (**4a**)*

mp 156-158 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05-8.03 (m, 2H), 7.58-7.55 (m, 1H), 7.48-7.44 (m, 2H), 7.34-7.32 (m, 2H), 7.29-7.26 (m, 3H), 6.16 (br s, 1H), 4.53 (d, J = 7.0 Hz, 1H), 4.33 (dd, J = 15.0, 7.0 Hz, 1H), 3.96-3.89 (m, 1H), 3.53 (dd, J = 9.6, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 173.6, 141.4, 136.3, 133.6, 129.5, 129.1, 128.6, 127.5,127 57.5,

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47.7, 43.4; FT-IR (neat) 3240, 2927, 1701, 1674, 1494, 1270, 1054, 757,698 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 266.1174, calcd for $C_{17}H_{16}NO_2$ 266.1176.

*(3S,4R)-3-Benzoyl-4-(thiophen-2-yl)pyrrolidin-2-one (**4c**)*

mp 77-79 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.4, 1.2 Hz, 2H), 7.60-7.57 (m, 1H), 7.49-7.46 (m, 2H), 7.17 (dd, J = 4.8, 1.5 Hz, 1H), 6.93-6.9 (m, 2H), 6.62 (br s, 1H), 4.64 (dd, J = 15.3, 7.6 Hz, 1H), 4.54 (d, J = 7.9 Hz, 1H), 3.94-3.91 (m, 1H), 3.56 (dd, J = 9.6, 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 172.4, 143.9, 136.3, 133.7, 129.5, 128.6, 127.1, 124.6 , 124.2, 58.4, 48.2, 39; FT-IR (neat) 3225, 2924, 1704, 1677, 1448, 1261, 1029, 750, 699 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 272.0741, calcd for $C_{15}H_{14}NO_2S$ 272.0740.

*(3S,4R)-3-Benzoyl-4-propylpyrrolidin-2-one (**4d**)*

mp >193 °C (compound decomposes above); ^1H NMR (500 MHz, $CDCl_3$) δ 8.08-8.06 (m, 2H), 7.61-7.57 (m, 1H), 7.51-7.48 (m, 2H), 6.40 (br s, 1H), 4.12 (d, J = 7.02 Hz, 1H), 3.64 (t, J = 8.24 Hz, 1H), 3.12-3.05 (m, 2H), 1.49 (q, J = 7.32 Hz, 2H), 1.29-1.24 (m, 2H), 0.88 (t, J = 7.32 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 174.0, 136.8, 133.6, 129.4, 128.7, 56.4, 46.6, 38.5, 36.5, 20.7, 14.1; FT-IR (neat) 3019, 2928, 1703, 1677, 1448, 1214, 1033, 748, 667 cm^{-1}; HRMS (ESI) $[M + Na]^+$ found *m/z* 254.1159, calcd for $C_{14}H_{17}NNaO_2$ 254.1151.

*2-Phenyl-3H-benzo[e]indole (**5**)*[22]

mp 135-137 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.67 (br s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.60-7.55 (m, 2H), 7.62-7.53 (m, 3H), 7.48-7.41 (m, 3H), 7.38-7.37 (m, 1H), 7.34-7.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136, 133.2, 132.4, 129.3, 129.2, 128.6, 128, 127.3, 125.8, 124.8, 124.3, 123.5, 123.3, 122.9, 112.5, 99.3; FT-IR (neat) 3372, 3019, 2927, 1719, 1604, 1284, 1214, 1074, 754 cm^{-1}; HRMS (ESI) $[M + H]^+$ found *m/z* 244.1125, calcd for $C_{18}H_{14}N$ 244.1121.

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ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of new compounds and X-ray crystallographic data for compound **4a** and **4l** (CIF).

AUTHOR INFORMATION

Corresponding Author

*E-mail: rsk@chem.unipune.ac.in

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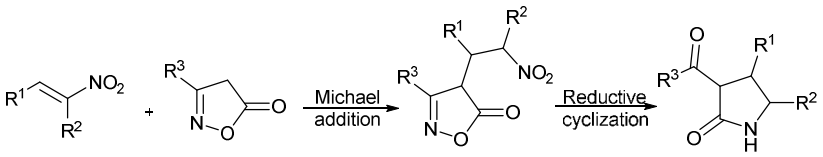
A Synthetic Route Towards 3, 4-disubstituted Pyrrolidin-2-ones via Michael Addition and Reductive Ring Closing Strategy

Monali Dawange, Nikita Parekh, Avinash Kumbhar, Wim Dehaen and Radhika Kusurkar*



2-Pyrrolidinone scaffolds with a wide range of substitution were synthesized with good yield and diastereoselectivity.