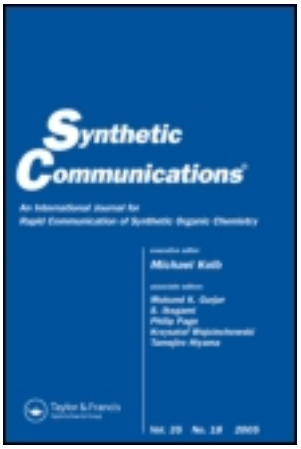

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A Practical and Efficient Synthesis of 2,5-Disubstituted-3,5-dihydro-imidazol-4-ones from Oxazolones

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A PRACTICAL AND EFFICIENT SYNTHESIS OF 2,5-DISUBSTITUTED-3,5-DIHYDRO-IMIDAZOL-4-ONES FROM OXAZOLONES

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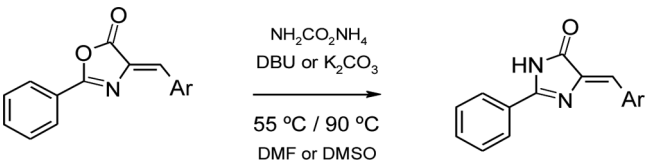
GRAPHICAL ABSTRACT



Abstract *An alternative procedure for the synthesis of 2,5-disubstituted-3,5-dihydro-imidazol-4-ones from substituted oxazolones was evaluated. The initial oxazolone ring-opening reaction was examined with a variety of ammonia source compounds followed by the subsequent 3,5-dihydro-imidazol-4-one cyclization reaction, which was carried out with either an organic or inorganic base in aprotic solvents. In this article, we report the results of an efficient and straightforward procedure for the synthesis of 2,5-disubstituted-3,5-dihydro-imidazol-4-ones that gives satisfactory yield and quality.*

Keywords Azlactone; DBU; Erlenmeyer reaction; imidazolone; oxazolone; potassium carbonate

INTRODUCTION

Unsaturated 2,5-disubstituted-3,5-dihydro-imidazol-4-ones are interesting compounds that have shown potential biological applications.[1] Therefore, these heterocycles have been the focused target intermediates of several groups in the field of combinatorial chemistry and drug discovery. The most common approaches to access these compounds are from oxazolones, glycine ester–imidic acid esters, and other condensation reactions.[2] As recently reported,[3] ammonium acetate was utilized as the source of ammonia in the synthesis of 2,5-disubstituted-3,5-dihydro-imidazol-4-ones using microwave techniques. The document states that the first stage of the reaction involves the oxazolone **1** ring opening by ammonia to give the carbamoyl

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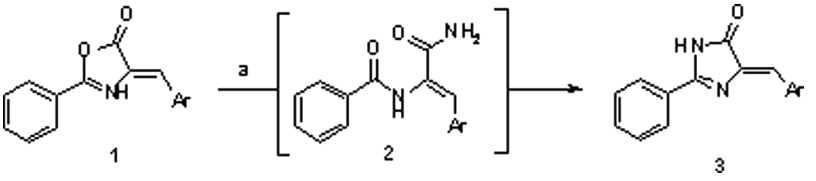


Scheme 1. Synthesis of 2,5-disubstituted-3,5-dihydro-imidazol-4-ones: (a) NH_4OAc, graphite, MW 600W.

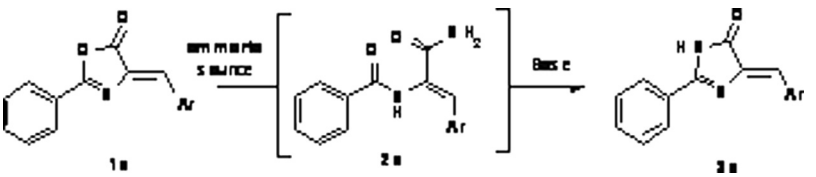
arylvinyl benzamide intermediate **2**, followed by an intramolecular condensation dehydration reaction to obtain the respective imidazolone **3** (Scheme 1). With this methodology as background, we attempted to develop an alternative procedure for the synthesis of these compounds using oxazolones as the starting material, which are readily available from the improved Erlenmeyer reaction in 2-methyl tetrahydrofuran (Me–THF).[4] At the same time, we hoped to demonstrate that this procedure could be suitable for scaling up to supply gram quantities of **3**.

RESULTS AND DISCUSSION

To find the best reaction conditions for the oxazolone ring-opening reaction, several ammonia candidates were tested, including ammonium acetate, formate, sulfamate, and carbamate (Scheme 2). It was found that the aminolysis reaction proceeded quickly to completion with ammonium acetate and ammonium carbamate. However, ammonium formate reacted very slowly, and ammonium sulfamate did not react at all (Table 1, entries 1–4). Therefore, ammonium acetate and carbamate were selected to proceed with the next step.

The intramolecular cyclization reaction has been previously reported in refluxing pyridine.[5] We found that running the reaction in Me-THF while using a stronger organic base, such as diisopropylethylamine (Hunig's base) or 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU), was also viable. However, DBU provided better conversion than Hunig's base (Table 2, entries 1 and 2).

The cyclization reaction with DBU proceeded faster when using intermediate **2a** from the ring-opening reaction with ammonium carbamate than **2a** from ammonium acetate (Table 2, entries 2 and 3). When the solvent was changed to dimethyiformamide (DMF), the rate of conversion to **3a** was greatly increased (1 h vs. 4 h) with the use of ammonium carbamate (Table 2, entries 4 and 5). In addition, when the cyclization reaction was examined with potassium carbonate (K_2CO_3) in dimethylsubfoxide (DMSO), similar results were obtained.



Scheme 2. Evaluation of reaction conditions for aminolysis and cyclization stages.

Table 1. Evaluation of ammonia source for oxazolone **1a** ring opening

			Aminolysis reaction	
Entry	Ammonium[a]	Solvent	Time (h)	Area (%)[b]
1	Acetate	Me-THF	1	97.3
2	Carbamate	Me-THF	1.5	94.2
3	Formate	Me-THF	8	90.3
4	Sulfamate	Me-THF	8	0

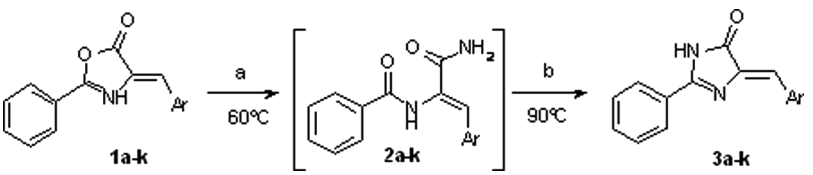
[a]Ammonia source = 2 equiv.
[b]Conversion by HPLC.

Based on these results, the ammonium carbamate–DBU–DMF procedure was tested with a variety of substituted oxazolones[4] (Scheme 3). The oxazolone (**1a–k**), ammonium carbamate, triethylamine (TEA), and DMF were combined at 55–60 °C, and after complete aminolysis, the carbamoyl intermediate (**2a–k**) was treated with DBU at 90 °C. Upon reaction completion, the mixture was diluted with water to allow the product to crystallize (Table 3, entries 1–11). The observed aminolysis reaction took 30 min; meanwhile, the imidazolone cyclization reaction took anywhere from 1 to 3 h. The overall yield ranged from 88 to 97%, with product quality >98 area% [high-performance liquid chromatography (HPLC)]. In a similar way, the ammonium carbamate–K_2CO_3–DMSO procedure was carried out with selected oxazolones including a gram-scale run (Table 3, entries 12–17).

Table 2. Organic base and solvent evaluation of imidazolone cyclization reaction

				Cyclization reaction	
Entry	Ammonium[a]	Solvent	Base	Time (h)	Area (%)[b]
1	Acetate	Me-THF	Hunig	12	49.6
2	Acetate	Me-THF	DBU	12	84.9
3	Carbamate	Me-THF	DBU	4	92.7
4	Acetate	DMF	DBU	10	70.6
5	Carbamate	DMF	DBU	1	96.7

[a]Ammonium source used for carbamoyl intermediate **2a**.
[b]Conversion by HPLC.



Scheme 3. General reaction conditions. Reagents: (a) $NH_2CO_2NH_4$ in DMF or DMSO; (b) DBU or K_2CO_3.

Table 3. General reaction conditions and results of the synthesis of 2,5-disubstituted-3,5-dihydro-imidazol-4-ones

Entry	Oxazolone 1, Ar=	Reaction time (h)		Isolated yield (%)	Imidazolone
		Aminolysis[a]	Cyclization[b]		
1	Ph-	0.5	1	92	**3a**
2	2-Cl-Ph-	0.5	1.5	90	**3b**
3	3-NO_2-Ph-	0.5	2	87	**3c**
4	4-F-Ph-	0.5	1.5	91	**3d**
5	4-Br-Ph-	0.5	1	94	**3e**
6	4-MeO-Ph-	0.5	1.5	92	**3f**
7	4-Me-Ph-	0.5	1	93	**3g**
8	4-NO_2-Ph-	0.5	1	88	**3h**
9	2-Thiophenyl-	0.5	2	93	**3i**
10	2-Furanyl-	0.5	1	89	**3j**
11	4-Diphenyl-	0.5	1	93	**3k**
12	Ph-	0.5	2[c]	92	**3a**
13	2-Cl-Ph-	0.5	1[c]	94	**3b**
14	3-NO_2-Ph-	0.5	1[c]	93	**3c**
15	4-Br-Ph-	1.0	1[c]	95	**3e**
16	2-Thiophenyl-	0.5	3[c]	95	**3i**
17	2-Furanyl-[d]	0.5	2[c]	94	**3j**

[a]0.8 mol% of ammonium carbamate.
[b]DBU as base (0.35 equiv except when noted).
[c]K_2CO_3 as base (0.5 equiv).
[d]Scale up run (20 g).

CONCLUSION

We have developed a practical and efficient method for the synthesis of 2,5-disubstituted-3,5-dihydro-imidazol-4-ones. Ammonium carbamate was an excellent source of ammonia at the oxazolone ring-opening stage, while the imidazolone cyclization stage was successfully executed using either DBU or potassium carbonate in an aprotic solvent. Both methods gave satisfactory product yield and quality.

EXPERIMENTAL

All chemicals were purchased from Alfa Aesar, Acros, and/or Aldrich. Melting points were determined in a Melt-Temp 3.0 Thermo Scientific apparatus at 5 °C/min. ^{1}H NMR and ^{13}C NMR were recorded on a 400-MHz Varian NMR. Reaction monitoring and product assay were performed on an Agilent Technologies 1200 HPLC instrument.

General DBU Procedure: 2-Phenyl-5-[1-phenylmethylidene]-3,5-dihydro-imidazol-4-one (3a)

A mixture of oxazolone **1a** (3.0 g, 12 mmol), DMF (9 mL), triethylamine (1 g, 10 mmol), and ammonium carbamate (0.75 g, 10 mmol) was heated to 55 °C and held for 30 min. The reaction was monitored for completion by HPLC. DBU (0.65 g, 4.2 mmol) was added to the solution via syringe, and the temperature was increased

to 90 °C and held for 1 h. Upon reaction completion, which was confirmed by HPLC, the mixture was cooled to 60–70 °C and water was added dropwise (35 mL) while keeping the temperature >60 °C. The orange slurry was slowly cooled to 20 °C and held for 2 h. 2-Phenyl-5-[1-phenylmethylidene]-3,5-dihydro-imidazol-4-one (**3a**) if was collected by vacuum filtration and washed with 1:5 methanol/water (5 °C) followed by water. The product was dried at 55 °C under vacuum for >12 h to give 2.74 g of a yellow solid (91%).

General Potassium Carbonate Procedure: 2-Pheny-5-[1-furan-2-yl-methylidene]-3,5-dihydro-imidazol-4-one (3j)

A mixture of 4-[1-Furan-2-yl-meth-(Z)-ylidene]2-phenyl-4H-oxazol-5one (**1j)** (20 g, 83.6 mmol), ammonium carbamate (5.22 g, 66.9 mmol), and DMSO (84 mL) was stirred at room temperature. Triethylamine (6.77 g, 66.9 mmol) was added, and the mixture was slowly heated to 55 °C for a 30 min hold before taking a sample for HPLC. Potassium carbonate (5.36 g, 41.8 mmol) was added to the dark solution, and the temperature was increased to 90–93 °C and held for 2 h. Upon reaction completion, confirmed by HPLC, the mixture was cooled to 60–65 °C, and water was added dropwise (165 mL) while keeping the temperature >60 °C. The brown slurry was held at 65 °C for 30 min and then slowly cooled to 20 °C. 2-Phenyl-5-[1-furan-2-yl-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (**3j)** if was collected by vacuum filtration and washed with 1:1 ethanol/water (−10 °C) followed by water. The product was dried at 65°C under vacuum for >12 h to give 18.8 g of a yellow solid (94%).

Data

2-Phenyl-5-[1-phenyl-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3a). Mp: found 277–278 °C; lit. 272–273 °C[3]; ^{1}H NMR (500 MHz, DMSO) δ 12.12 (s, 1H), 8.33 (d, $J = 7.4$, 2H), 8.19 (d, $J = 7.1$, 2H), 7.66 (t, $J = 7.2$, 1H), 7.61 (t, $J = 7.3$, 2H), 7.50 (t, $J = 7.4$, 2H), 7.44 (t, $J = 7.3$, 1H), 7.05 (s, 1H); ^{13}C NMR (126 MHz, DMSO) δ 172.50, 161.36, 140.92, 134.83, 133.02, 132.53, 130.46, 129.49, 129.21, 128.42, 127.87, 125.52.

2-Phenyl-5-[1-(2-chlorophenyl)-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3b). Mp: found 262–263 °C; lit. (268–269 °C)[6]; ^{1}H NMR (500 MHz, DMSO) δ 12.27 (s, 1H), 9.05 (d, $J = 7.9$, 1H), 8.20 (d, $J = 7.3$, 2H), 7.68 (t, $J = 7.3$, 1H), 7.64–7.57 (m, 3H), 7.52 (t, $J = 7.5$, 1H), 7.45 (t, $J = 6.9$, 1H), 7.30 (s, 1H); ^{13}C NMR (126 MHz, DMSO) δ 172.42, 162.98, 142.27, 135.28, 133.51, 133.41, 132.13, 131.74, 130.23, 129.53, 128.15, 128.10, 128.06, 118.82.

2-Phenyl-5-[1-(3-nitrophenyl)-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3c). Mp: found 249–250 °C; lit. (261–262 °C)[7]; ^{1}H NMR (500 MHz, DMSO) δ 12.25 (s, 1H), 9.32 (s, 1H), 8.63 (d, $J = 7.8$, 1H), 8.23 (d, $J = 8.2$, 1H), 8.20 (d, $J = 7.1$, 2H), 7.76 (t, $J = 8.0$, 1H), 7.69 (t, $J = 7.3$, 1H), 7.63 (t, $J = 7.3$, 2H), 7.16 (s, 1H); ^{13}C NMR (126 MHz, DMSO) δ 172.25, 162.94, 148.56, 142.63, 138.30, 136.50, 133.46, 130.58, 129.55, 128.09, 128.03, 126.29, 124.26, 122.35.

2-Phenyl-5-[1-(4-fluorophenyl)-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3d). Mp: found 274–276 °C; ^{1}H NMR (500 MHz, DMSO) δ 12.11 (s, 1H),

8.40 (dd, $J = 5.9$, 8.8, 2H), 8.17 (d, $J = 7.0$, 2H), 7.64 (t, $J = 7.3$, 1H), 7.60 (d, $J = 7.7$, 2H), 7.32 (t, $J = 8.9$, 2H), 7.05 (s, 1H); ^{13}C NMR (126 MHz, DMSO) δ 172.43, 164.30, 162.31, 161.42, 140.53, 134.88, 134.82, 133.01, 131.54, 129.46, 128.38, 127.85, 124.27, 116.40, 116.22. Anal. calcd. for $C_{16}H_{11}FN_2O$: C, 72.17; H, 4.16; F, 7.13; O, 6.01; N, 10.52. Found: C, 71.66; H, 3.89; F, 7.37; O, 6.23; N, 10.43.

2-Phenyl-5-[1-(4-bromophenyl)-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3e). Mp: found 318–321 °C; ^{1}H NMR (500 MHz, DMSO) δ 12.15 (s, 1H), 8.27 (d, $J = 8.6$, 2H), 8.19 (d, $J = 7.1$, 2H), 7.70 (d, $J = 8.6$, 2H), 7.67 (t, $J = 7.9$, 1H), 7.61 (t, $J = 7.4$, 2H), 7.02 (s, 1H); ^{13}C NMR (126 MHz, DMSO) δ 172.37, 161.82, 141.40, 139.90, 134.23, 134.08, 133.17, 132.24, 129.50, 128.31, 127.95, 123.98. Anal. calcd. for $C_{16}H_{11}BrN_2O$: C, 58.74; H, 3.39; Br, 24.42; O, 4.89; N, 8.56. Found: C, 58.37; H, 3.00; Br, 24.24; O, 5.03; N, 8.42.

2-Phenyl-5-[1-(4-methoxyphenyl)-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3f). Mp: found 292–294 °C; lit. (289–290°C)[3]; ^{1}H NMR (500 MHz, DMSO) δ 12.02 (s, 1H), 8.31 (d, $J = 8.9$, 2H), 8.17 (d, $J = 6.7$, 2H), 7.63 (t, 1H), 7.60 (t, $J = 7.1$, 2H), 7.08 (d, $J = 9.0$, 2H), 7.02 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 172.42, 161.34, 159.92, 139.02, 134.51, 132.67, 129.43, 128.62, 127.64, 127.60, 125.85, 114.89, 55.81.

2-Phenyl-5-[1-(4-methylphenyl)-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3g). Mp: found 302–304 °C; lit. (288–289 °C)[3]; ^{1}H NMR (500 MHz, DMSO) δ 12.07 (s, 1H), 8.22 (d, $J = 8.2$, 2H), 8.17 (d, $J = 6.9$, 2H), 7.65 (t, $J = 7.2$, 1H), 7.60 (t, $J = 7.2$, 2H), 7.31 (d, $J = 8.1$, 2H), 7.01 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (126 MHz, DMSO) δ 172.47, 160.73, 140.62, 140.21, 132.87, 132.57, 132.14, 129.91, 129.47, 128.51, 127.77, 125.77, 21.70.

2-Phenyl-5-[1-(4-nitrophenyl)-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3h). Mp: found 303–304 °C; lit. (325–327 °C)[7]; ^{1}H NMR (500 MHz, DMSO) δ 12.29 (s, 1H), 8.56 (d, $J = 9.0$, 2H), 8.30 (d, $J = 9.0$, 2H), 8.23 (d, $J = 7.1$, 2H), 7.69 (t, $J = 7.3$, 1H), 7.63 (t, $J = 7.5$, 2H), 7.11 (s, 1H); ^{13}C NMR (126 MHz, DMSO) δ 172.32, 163.70, 147.53, 143.49, 141.39, 133.63, 133.12, 129.53, 128.26, 128.02, 124.15, 121.97.

2-Phenyl-5-[1-thiophen-2-yl-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3i). Mp: found 310–311 °C; lit. (291–292 °C)[3]; ^{1}H NMR (500 MHz, DMSO) δ 12.07 (s, 1H), 8.17 (d, $J = 6.7$, 2H), 7.92 (d, $J = 5.1$, 1H), 7.74 (d, $J = 3.6$, 1H), 7.66–7.57 (m, 3H), 7.40 (s, 1H), 7.20 (t, 1H); ^{13}C NMR (126 MHz, DMSO) δ 171.55, 159.62, 138.54, 138.43, 135.27, 135.06, 132.80, 129.48, 128.44, 128.17, 127.70, 119.92.

2-Phenyl-5-[1-furan-2-yl-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3j). Mp: found 263–264 °C; Lit. (266–267 °C)[3]; ^{1}H NMR (500 MHz, DMSO) δ 12.09 (s, 1H), 8.17 (d, $J = 7.0$, 2H), 7.98 (d, $J = 1.7$, 1H), 7.64 (t, $J = 7.3$, 1H), 7.58 (t, $J = 4.5$, 11.5, 2H), 7.56 (t, 1H), 6.89 (s, 1H), 6.79 (d, $J = 3.5$, 1H); ^{13}C NMR (126 MHz, DMSO) δ 171.84, 160.49, 151.19, 146.83, 138.39, 132.89, 129.45, 128.40, 127.81, 118.71, 114.21, 112.69.

2-Phenyl-5-[1-biphenyl-4-yl-meth-(Z)-ylidene]-3,5-dihydro-imidazol-4-one (3k). Mp: found 300–302 °C; ^{1}H NMR (500 MHz, DMSO) δ 12.13 (s, 1H), 8.42

(d, j = 8.4, 2H), 8.21 (d, $J = 6.9$, 2H), 7.83 (d, $J = 8.5$, 2H), 7.77 (d, $J = 7.2$, 2H), 7.69–7.59 (m, 3H), 7.51 (t, $J = 7.7$, 2H), 7.41 (t, $J = 7.3$, 1H), 7.09 (s, 1H), 3.32 (s, 2H); ^{13}C NMR (126 MHz, DMSO) δ 172.44, 161.26, 141.76, 140.94, 139.74, 134.04, 133.15, 133.02, 129.52, 129.51, 128.47, 128.45, 127.86, 127.38, 127.20, 125.06. Anal. Calcd. for $C_{22}H_{16}N_2O$: C, 81.46; H, 4.97; O, 4.93; N, 8.64. Found: C, 80.88; H, 4.70; O, 5.06; N, 8.59.

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