# Synthesis of a Library of Imidazolin-4-ones Using Poly(ethylene glycol) as Soluble Support

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**Abstract:** A library of imidazolin-4-ones has been synthesized using poly(ethylene glycol) (PEG) as soluble polymer support. The imidazolin-4-ones **6** or **7** were synthesized effectively by reaction of primary amine with PEG-supported carbodiimides **4**, which were obtained from aza-Wittig reaction of PEG-supported iminophosphoranes **3** with isocyanates.

**Key words:** poly(ethylene glycol), polymer-supported, aza-Wittig reaction, imidazolin-4-one, ylides

Imidazolin-4-ones have received considerable attention over the last few years due to their interesting biological activities. Some of them have exhibited promising pharmacological activities,[1] others have been shown to possess good herbicidal activities, such as imazamethabenz and imazethapyr.[2] They are also a key structural skeleton in some alkaloids.[3] Hence these heterocycles, in particular 2,3,5-trisubstituted imidazolin-4-ones, have become attractive combinatorial chemistry libraries in drug discovery and crop protection.

There are many known methods for the synthesis of imidazolin-4-ones, including the aza-Wittig reaction.[4] Recently several approaches to access this class of compounds based on solid-phase synthesis have been reported.[5] However, there is still no report on the use of soluble polymer support to prepare these molecules.

Currently, liquid-phase synthesis using soluble polymers technique has attracted widespread interest in the field of combinatorial chemistry.[6] It possesses both the advantages of conventional liquid-phase synthesis and solid-phase synthesis. Moreover, the soluble polymer-bound species allow using routine analytical methods ($^1$H NMR, TLC or IR) the monitoring of the reaction progress and determining the structures of products attached to polymer support directly. Poly(ethylene glycol) (PEG) is an ideal support and the most widely used polymer for liquid-phase combinatorial synthesis in terms of its controllable solubility in different solvents. Recently we have been interested in the synthesis of imidazolinones, quinazolinones and thienopyrimidinones via aza-Wittig reaction of α- or β-ethoxycarbonyl iminophosphorane with aromatic isocyanate and subsequent reaction with various nucleophiles under mild conditions.[7] Herein we wish to report an efficient synthesis of imidazolin-4-ones from PEG-supported iminophosphorane in parallel fashion. Commercially available, inexpensive difunctional PEG-4000 was chosen as a soluble polymer support in this study.

As shown in Scheme 1, chloroacetyl chloride was added dropwise to the soluble support PEG 4000 in the presence of $Et_3N$ in anhydrous MeCN at 0 °C. The mixture was then heated to refluxing temperature for 24 hours. The resulting PEG-supported alkyl chloride **1** was obtained by precipitation in diethyl ether in 95% yield. A solution of **1** in anhydrous MeCN was then treated with sodium azide under nitrogen atmosphere and the mixture was heated for 20 hours at reflux. Similarly, the PEG-supported azide **2** was obtained by precipitation in diethyl ether.[8] Further reaction of **2** with triphenylphosphine furnished the PEG-supported iminophosphorane **3**, which was allowed to react with aromatic isocyanates to produce PEG-supported carbodiimides **4** via intermolecular aza-Wittig reaction.[9]

**Table 1** Liquid-Phase Synthesis of Imidazolin-4-ones by aza-Wittig Reaction

| Entry | Product | Ar | R | Conditions | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | **6a** | Ph | *i*-Pr | r.t./5 h | 45 |
| | **7a** | Ph | *i*-Pr | r.t./5 h | 40 |
| 2 | **6b** | Ph | *c*-Hex | r.t./5 h | 44 |
| | **7b** | Ph | *c*-Hex | r.t./5 h | 38 |
| 3 | **6c** | Ph | *n*-Pr | r.t./2 h | 91 |
| 4 | **6d** | Ph | *n*-Bu | r.t./2 h | 88 |
| 5 | **6e** | Ph | *i*-Bu | r.t./3 h | 84 |
| 6 | **6f** | Ph | $PhCH_2$ | r.t./2 h | 78 |
| 7 | **6g** | Ph | H[b] | r.t./1 h | 85 |
| 8 | **6h** | Ph | Me | r.t./1 h | 92 |
| 9 | **6i** | Ph | Et | r.t./1 h | 87 |
| 10 | **6j** | 3-$MeC_6H_4$ | H[b] | r.t./1 h | 82 |
| 11 | **6k** | 3-$MeC_6H_4$ | Me | r.t./1 h | 86 |
| 12 | **6l** | 3-$MeC_6H_4$ | Et | r.t./1 h | 80 |

[a] Isolated yields based on PEG-supported carbodiimide **4**.
[b] Concentrated ammonia solution was used.

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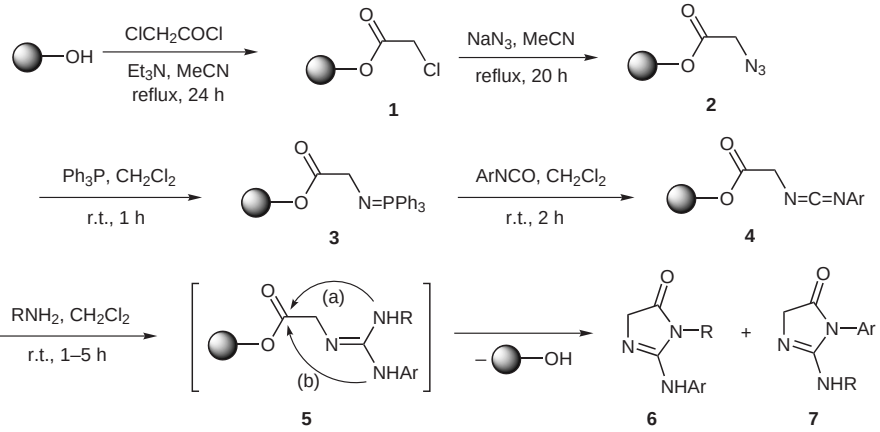


**Scheme 1** Synthesis of imidazolin-4-ones **6** or **7** using poly(ethylene glycol) as soluble support

However, when alkyl isocyanates were reacted with iminophosphorane **3**, the corresponding carbodiimides were not obtained probably due to dimerization or polymerization.[10]

With the PEG-supported carbodiimides **4** in hand, we switched our attention to its application in liquid-phase combinatorial synthesis. After the PEG-supported carbodiimides **4** reacted with primary amine at room temperature, the cleaved PEG support was precipitated by addition of diethyl ether and separated by simple filtration. The imidazolin-4-ones **6** or **7** were obtained by recrystallization from a solvent mixture of hexane and dichloromethane (1:1–1:3) or by column chromatography on silica gel [EtOAc–petroleum ether (1:2) as the eluent].[11] In some cases, a trace amount of the PEG residue and $Ph_3PO$ was present together with the final products **6** or **7**. This problem could be easily solved by passing the crude product through a pad of silica gel using EtOAc–petroleum ether (1:3–1:1) as the eluent. A variety of primary amines and isocyanates could be used for this synthetic strategy and the products were obtained in good yields (Table 1).

As can be seen in Scheme 1, reaction between the PEG-supported carbodiimides **4** with primary amine should afford the PEG-supported guanidine intermediates **5**. From these intermediates **5**, the formation of two regioisomeric imidazolin-4-ones **6** (pathway a) or **7** (pathway b) could take place. When primary amines with functional groups such as *n*-propyl, *n*-butyl, benzyl, methylamine, etc. (Table 1, entries 3–12) were used, regioselective cyclization with the formation of 2-arylaminoimidazolin-4-one **6** took place. However, for primary amines having functional groups like isopropyl and cyclohexylamine (Table 1, entries 1 and 2), both of the products **6** and **7** were formed. The results indicated that for this type of transformation, regioselectivity toward the formation of **6** seemed to be influenced not only by the difference in the nucleophilic character of the two nitrogen atoms of the guanidine intermediate **5**, but also by steric factor. Thus, when nucleophilic, sterically non-hindered primary amines were used, 2-arylamino-imidazolin-4-ones **6** were formed as the sole product. However, when steric hindrance was present in the intermediate **5**, a mixture of **6** and **7** was obtained.

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(8) **PEG-Supported Azide 2**. A mixture of PEG-supported chloride **1** (10 mmol) and sodium azide (0.78 g, 12 mmol) in anhyd MeCN (100 mL) was stirred for 20 h at reflux under a nitrogen atmosphere. The mixture was filtered, the filtrate was condensed and $Et_2O$ was added to precipitate the PEG-supported azides **2**. $^1$H NMR (400 MHz, $CDCl_3$): δ = 3.47–3.82 (s, PEG-$OCH_2CH_2O$), 3.92 (s, 2 H, $CH_2N$), 4.34 (t, *J* = 6.4 Hz, 2 H, PEG-$OCH_2CH_2OCO$). IR (KBr): 2108 ($N_3$), 1744 (C=O), 1242 cm$^{-1}$.

(9) **PEG-Supported Carbodiimide 4a**. A solution of triphenylphosphine (2.62 g, 10 mmol) in anhyd $CH_2Cl_2$ (10 mL) was added dropwise under nitrogen at r.t. to a well-stirred solution of the PEG-supported azide **2** (10 mmol) in anhyd $CH_2Cl_2$ (100 mL). The reaction mixture was stirred at r.t. for 1 h, then phenyl isocyanate (1.19 g, 10 mmol) was added at 0 °C. After the reaction mixture was stirred at r.t. for 2 h, the solvent was removed under reduced pressure. The PEG-supported carbodiimide **4a** (Ar = Ph) was precipitated by addition of $Et_2O$ and was separated by simple filtration. $^1$H NMR (400 MHz, $CDCl_3$): δ = 3.48–3.64 (m, PEG-$OCH_2CH_2O$), 3.82 (s, 2 H, $NCH_2COO$), 4.30 (t, *J* = 6.4 Hz, 2 H, PEG-$CH_2OCO$). IR (KBr): 2144 (N=C=N), 1753 (C=O), 1242 cm$^{-1}$.

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(11) **Imidazolin-4-ones 6 and 7**: A solution of primary amine (2 mmol) in $CH_2Cl_2$ (5 mL) was added to PEG-supported carbodiimide **4** (2 mmol) in $CH_2Cl_2$ (10 mL), and the mixture was stirred for the time shown in Table 1 at r.t. The PEG was precipitated by addition of $Et_2O$ and was separated by simple filtration. The imidazolin-4-ones were obtained by recrystallization from a solvent mixture of hexane and $CH_2Cl_2$ (1:1–1:3) or by column chromatography on silica gel (EtOAc–PE, 1:3–1:1). Spectral data for imidazolin-4-ones **6** and **7**: **6a**: white crystals; mp 130–131 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 7.2 Hz, 6 H, 2 × Me), 3.84 (s, 2 H, $CH_2$), 4.57–4.61 (m, 2 H, NH, CH), 6.97–7.34 (m, 5 H, ArH). MS: *m*/*z* (%) = 217 (32) [M$^+$], 174 (100), 118 (77), 146 (30), 106 (48). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.03; H, 7.12; N, 19.38. **7a**: white crystals; mp 101–102 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.17–1.22 (m, 6 H, 2 × Me), 3.79–4.02 (m, 2 H, NH, CH), 4.20–4.25 (m, 2 H, $CH_2$), 7.24–7.57 (m, 5 H, ArH). MS: *m*/*z* (%) = 217 (11) [M$^+$], 174 (66), 118 (100). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.41; H, 7.05; N, 19.11. **6b**: white crystals; mp 132–134 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.22–2.38 (m, 10 H, 5 × $CH_2$), 3.81 (s, 2 H, $CH_2$), 4.14–4.21 (m, 1 H, CH), 4.53 (s, 1 H, NH), 6.94–7.33 (m, 5 H, ArH). MS: *m*/*z* (%) = 257 (6) [M$^+$], 176 (88), 131 (10), 118 (100). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.25; H, 7.41; N, 16.24. **7b**: white crystals; mp 92–93 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.07–2.04 (m, 10 H, 5 × $CH_2$), 3.73 (s, 1 H, NH), 3.80–3.90 (m, 1 H, CH), 4.22 (s, 2 H, $CH_2$), 7.25–7.55 (m, 5 H, ArH). MS: *m*/*z* (%) = 257 (5) [M$^+$], 202 (3), 174 (100), 146 (15), 119 (70). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.17; H, 7.57; N, 16.18. **6c**: white crystals; mp 76–77 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3 H, Me), 1.73–1.82 (m, 2 H, $CH_2$), 3.66 (t, *J* = 7.2 Hz, 2 H, $NCH_2$), 3.91 (s, 2 H, $CH_2$), 4.58 (s, 1 H, NH), 6.98–7.34 (m, 5 H, ArH). MS: *m*/*z* (%) = 217 (54) [M$^+$], 174 (100), 118 (85). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.45; H, 6.78; N, 19.38. **6d**: white crystals; mp 46–47 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H, Me), 1.37–1.73 (m, 4 H, $CH_2CH_2$), 3.69 (t, *J* = 7.2 Hz, 2 H, $NCH_2$), 3.89 (s, 2 H, $CH_2$), 4.60 (s, 1 H, NH), 6.96–7.33 (m, 5 H, ArH). MS: *m*/*z* (%) = 231 (58) [M$^+$], 202 (18), 188 (58), 176 (64), 146 (33), 100 (100). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.42; H, 7.36; N, 18.22. **6e**: white crystals; mp 82–84 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.8 Hz, 6 H, 2 × Me), 2.20–2.30 (m, 1 H, CH), 3.51 (d, *J* = 7.6 Hz, 2 H, $NCH_2$), 3.90 (s, 2 H, $CH_2$), 4.60 (s, 1 H, NH), 6.95–7.33 (m, 5 H, ArH). MS: *m*/*z* (%) = 231 (7) [M$^+$], 176 (100), 119 (32), 106 (28). Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.47; H, 7.53; N, 18.36. **6f**: white crystals; mp 87–88 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 2 H, $CH_2$), 4.65 (s, 1 H, NH), 4.87 (s, 2 H, $NCH_2$), 6.96–7.54 (m, 10 H, ArH). MS: *m*/*z* (%) = 265 (7) [M$^+$], 236 (9), 207 (21), 160 (38), 91 (100). Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84. Found: C, 72.28; H, 5.61; N, 15.98. **6g**: white crystals; mp 264–266 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 3.74 (s, 2 H, $CH_2$), 7.05–7.49 (m, 5 H, ArH), 7.55 (s, 1 H, NH), 9.92 (s, 1 H, NH). MS: *m*/*z* (%) = 175 (83) [M$^+$], 146 (112), 118 (100). Anal. Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.95; H, 5.17; N, 23.93. **6h**: white crystals; mp 97–98 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 2.98 (s, 3 H, NMe), 3.84 (s, 2 H, $CH_2$), 7.02 (s, 1 H, NH), 6.95–7.29 (m, 5 H, ArH). MS: *m*/*z* (%) = 189 (92) [M$^+$], 160 (62), 132 (100). Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.41; H, 5.71; N, 22.36. **6i**: white crystals; mp 113–114 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.2 Hz, 3 H, Me), 3.77 (q, *J* = 7.2 Hz, 2 H, $NCH_2$), 3.91 (s, 2 H, $CH_2$), 4.60 (s, 1 H, NH), 7.01–7.34 (m, 5 H, ArH). MS: *m*/*z* (%) = 203 (51) [M$^+$], 174 (36), 160 (63), 146 (21), 104 (100). Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.25; H, 6.57; N, 20.60. **6j**: white crystals; mp 253–255 °C. $^1$H NMR (400 MHz, DMSO-$d_6$): δ = 2.29 (s, 3 H, Me), 3.86 (s, 2 H, $CH_2$), 6.75–7.24 (m, 4 H, ArH), 7.53 (s, 1 H, NH), 9.86 (s, 1 H, NH). MS: *m*/*z* (%) = 203 (46) [M$^+$], 174 (45), 160 (9), 146 (100), 91 (60). Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.31; H, 5.94; N, 22.02. **6k**: white crystals; mp 108–109 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, Me), 3.17 (s, 3 H, Me), 3.91 (s, 2 H, $CH_2$), 4.60 (s, 1 H, NH), 6.78–7.22 (m, 4 H, ArH). MS: *m*/*z* (%) = 203 (45) [M$^+$], 174 (45), 146 (100), 118 (41). Anal. Calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.13; H, 6.59; N, 20.53. **6l**: white crystals; mp 101–102 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.2 Hz, 3 H, Me), 2.33 (s, 3 H, Me), 3.75 (q, *J* = 7.2 Hz, 2 H, $NCH_2$), 3.90 (s, 2 H, $CH_2$), 4.64 (s, 1 H, NH), 6.79–7.20 (m, 4 H, ArH). MS: *m*/*z* (%) = 217 (100) [M$^+$], 188 (48), 174 (94), 160 (21), 118 (82). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.31; H, 6.82; N, 19.46.