A SOLUTION-PHASE PARALLEL SYNTHESIS OF 2-AMINO-5-FURFURYLIDENE-4H-IMIDAZOLIN-4-ONES

Ming-Wu Ding*, Shang-Jun Yang, Yong Sun, Zhao-Jie Liu, Xiao-Peng Liu
Institute of Organic Synthesis, Central China Normal University, Wuhan, 430079, P. R. China

Abstract: 2-Amino-5-furfurylidene-4H-imidazolin-4-ones 4 were rapidly prepared by a solution-phase parallel synthetic method, which includes aza-Wittig reaction of iminophosphorane 1 with phenyl isocynate to give carbodiimide 2 and subsequent reaction of 2 with various amine in a parallel fashion.

Introduction

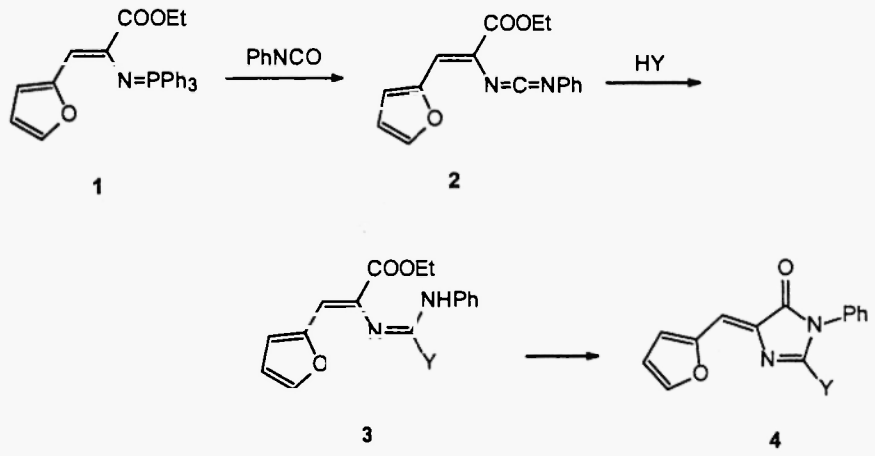
4H-Imidazolin-4-ones are important heterocycles having biological activities(1-3). Some derivatives of 5-furfurylidene-4H-imidazolin-4-one were found to show good antiinflammatory activity(4). They can be synthesized from condensation of furfural with 5-unsubsituted 4H-imidazolin-4-ones or from corresponding oxazolones(5,6). However, there were few reports on the synthesis of 2-amino substituted 5-furfurylidene- 4H-imidazolin-4-ones(5).

Recently, combinatorial synthesis of libraries containing small organic molecules has become a rapid evolving area of research(7,8). It includes solid-phase and solution-phase synthetic techniques. Although some solid phase synthetic methods for 4H-imidazolin-4-one have been reported(9,10), there is no solution phase synthetic route to 4H-Imidazolin-4-ones. In our work on synthesis of biologically active imidazolinones, we developed a facile synthesis of 2-amino-4H-imidazolin-4-ones(11,12). Here we wish to report further an efficient solution-phase parallel synthesis of some unreported derivatives of 2-amino-5-furfurylidene- 4H-imidazolin-4-ones 4. By using this parallel synthetic method, 4 was rapidly obtained and the separation of 4 from the reaction mixture was easily carried out by simple recrystallization.

Results and Discussion

The vinyliminophosphorane 1 reacted with phenyl isocyanates to give carbodiimide 2. After removing the by-product Ph_3PO by recrystallization, the solution of 2 was divided equally into several parts to which were added various amines separately. The resulted solution was stood at room temperature for 5-24 hours and then recrystallized to give imidazolinones 4 in satisfactory yields. The formation of 4 can be rationalized in terms of an initial nucleophilic addition to give the guanidine intermediate 3, which cyclized to give 4. When HY is secondary amine, the reaction can be carried out at room temperature even as Y is bulky di-*iso*-propylamine. When HY is primary amine, the cyclization was achieved at room temperature and only 4 can be isolated from the reaction mixture in moderate to good yields(11). The results are

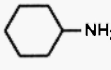
listed in Table 1.



Scheme 1

The structure of 4 has been confirmed by spectral data ^{1}H NMR, IR and MS. For example, the ^{1}HNMR spectrum data in **4g** showed the signals of NH at 4.56ppm as a wide absorption and NCH_2 at 3.41~3.58ppm as multiple absorption, which strongly suggested the existing of $NHCH_2CH_2CH_3$ group in **4g**. The other signals

Table 1 Preparation of 4H-imidazolin-4-ones 4.

Compound	HY	Condition	Yield(%)*
4a	$HNEt_2$	r.t./6hr	84
4b	$HN(n\text{-}Pr)_2$	r.t./6hr	81
4c	$HN(sec\text{-}Bu)_2$	r.t./12hr	71
4d	$N(i\text{-}Pr)_2$	r.t./24hr	72
4e		r.t./6hr	87
4f		r.t./6hr	85
4g	$n\text{-}PrNH_2$	r.t./5hr	53
4h	$n\text{-}BuNH_2$	r.t./5hr	51
4i		r.t./12hr	76
4j	$PhCH_2NH_2$	r.t./10hr	68

*isolated yields based on iminophosphorane 1

appeared at 7.54~6.50 (m, 8H, Ph-H and Furfuryl-H), 6.71 (s, 1H, olefinic hydrogen), 1.75~1.57 (m, 2H, CH_2) and 0.96 (t,

3H, J=7.3Hz, CH_3). The IR of **4g** showed the strong stretching resonance peak of imidazolinone C=O at 1715 cm^{-1} and the peak of C=C or C=N at about 1659 cm^{-1} or 1582 cm^{-1}. The signal at about 3342 cm^{-1} is due to the stretching resonance of N-H. The MS of **4g** showed M^+ at m/z 295 with 35% abundance.

In summary, the above solution-phase parallel synthetic method provides a high-speed synthesis of 2-amino-5-furfurylidene-4H-imidazolin-4-ones. Due to the easily accessible and versatile starting material, this method has the potential in synthesis of many biologically and pharmaceutically active imidazolinone derivatives.

Experimental

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a PE-983 infrared spectrometer. NMR were taken on a Varian XL-200 spectrometer. Iminophosphorane **1** was prepared by the literature report(13).

Parallel Synthesis of 2-Amino-5-furfurylidene-4H-imidazolin-4-ones **4**-To a solution of vinyliminophos- phorane **1** (13.2g, 30mmol) in dry methylene dichloride (100mL) was added phenyl isocyanate (3.57g, 30mmol) under nitrogen at room temperature. After the reaction mixture was stood for 6 hours, the solvent was removed off under reduced pressure and ether/petroleum ether (1:2, 200mL) was added to precipitate triphenylphosphine oxide. Filtered, the filtrate was condensed and methylene dichloride was added to make a solution of carbodiimide **2** (100mL), which was divided into ten parts (10mL every part). To each part of **2** prepared above (10mL) was added separately diethylamine (0.31mL, 3mmol), or di-*n*-propylamine (0.42mL, 3mmol), or di-*iso*-butylamine (0.52mL, 3mmol), or di-*iso*-propylamine (0.43mL, 3mmol), or piperidine (0.30mL, 3mmol), or morpholine (0.26mL, 3mmol), or *n*-propyl amine (0.25mL, 3mmol), or *n*-butylamine (0.30mL, 3mmol), or cyclohexylamine (0.34mL, 3mmol), or phenylmethylamine (0.33mL, 3mmol). After the reaction mixture was stood for 5~24 hours, the solvent was removed off under reduced pressure and the residual was recrystallized from methylene dichloride/ petroleum ether to give 4H-imidazolin-4-ones **4a**~**4j** separately.

4a: yellow crystals, m. p. 144~146℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.44~6.50 (m, 8H, Ar-H), 6.68 (s, 1H, =CH), 3.27 (q, 4H, J=7.7Hz, $2NCH_2$), 1.08 (t, 6H, J=7.2Hz, $2CH_3$); IR (KBr, cm^{-1}), 1721 (C=O), 1643 (C=C), 1565 (C=N), 1427, 1346, 1237; MS (m/z, %), 309 (M^+, 100), 280 (96), 266 (72), 253 (54), 205 (94), 190 (90), 175 (89), 119 (91).

4b: yellow crystals, m. p. 115~116℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.44~6.51 (m, 8H, Ar-H), 6.67 (s, 1H, =CH), 3.15 (t, 4H, J=7.8Hz, $2NCH_2$), 1.60~1.49 (m, 4H, $2CH_2$), 0.73 (t, 6H, J=7.8Hz, $2CH_3$); IR (KBr, cm^{-1}), 1723 (C=O), 1643 (C=C), 1571 (C=N), 1431, 1356, 1235; MS (m/z, %), 337 (M^+, 100), 308 (28), 294 (70), 266 (98), 253 (76), 219 (81), 190 (90), 105 (97).

4c: yellow crystals, m. p. 177~179℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.45~6.50 (m, 8H, Ar-H), 6.67 (s, 1H, =CH), 3.04 (d, 4H, J=7.8Hz, $2NCH_2$), 2.10~1.90 (m, 2H, 2CH), 0.82 (d, 12H, J=5.8Hz, $4CH_3$); IR (KBr, cm^{-1}), 1715 (C=O), 1640 (C=C), 1557 (C=N), 1425, 1238; MS (m/z, %), 365 (M^+, 17), 309 (10), 266 (100), 238 (15), 131 (33), 106 (42).

4d: yellow crystals, m. p. 188~190℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.43~6.49 (m, 8H, Ar-H), 6.66 (s, 1H, =CH), 3.70~3.58 (m, 2H, 2CH), 1.30 (d, 12H, J=6.8Hz, $4CH_3$); IR (KBr, cm^{-1}), 1721 (C=O), 1633 (C=C), 1556 (C=N), 1427, 1369, 1244; MS (m/z, %), 337 (M^+, 67), 294 (100), 280 (39), 253 (23), 145 (16), 119 (64).

4e: yellow crystals, m. p. 194~196℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.47~6.51 (m, 8H, Ar-H), 6.73 (s, 1H, =CH), 3.38~3.22 (m, 4H, $2NCH_2$), 1.60~1.38 (m, 6H, $3CH_2$); IR (KBr, cm^{-1}), 1713 (C=O), 1637 (C=C), 1566 (C=N), 1437, 1355, 1275; MS (m/z, %), 321 (M^+, 100), 292 (15), 230 (6), 187 (24), 131 (32), 106 (21).

4f: yellow crystals, m. p. 217~219℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.49~6.51 (m, 8H, Ar-H), 6.80 (s, 1H, =CH), 3.64

(t, 4H, J=4.9Hz, $2OCH_2$), 3.33 (t, 4H, J=4.4Hz, $2NCH_2$); IR (KBr, cm^{-1}), 1720 (C=O), 1640 (C=C), 1556 (C=N), 1427, 1266; MS (m/z, %), 323 (M^+, 100), 266 (17), 238 (8), 189 (30), 145 (30), 77 (77).

4g: yellow crystals, m. p. 166~168℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.54~6.50 (m, 8H, Ar-H), 6.71 (s, 1H, =CH), 4.56 (s, 1H, NH), 3.41~3.58 (m, 2H, NCH_2), 1.75~1.57 (m, 2H, CH_2), 0.96 (t, 3H, J=7.3Hz, CH_3); IR (KBr, cm^{-1}), 3342 (N-H), 1715 (C=O), 1659 (C=C), 1582 (C=N), 1373, 1237; MS (m/z, %), 295 (M^+, 35), 266 (9), 253 (46), 161 (9), 119 (100), 106 (72).

4h: yellow crystals, m. p. 142~144℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.52~6.51 (m, 8H, Ar-H), 6.70 (s, 1H, =CH), 4.55 (s, 1H, NH), 3.43~3.59 (m, 2H, NCH_2), 1.70~1.28 (m, 4H, CH_2CH_2), 0.94 (t, 3H, J=7.2Hz, CH_3); IR (KBr, cm^{-1}), 3340 (N-H), 1717 (C=O), 1655 (C=C), 1580 (C=N), 1372, 1238; MS (m/z, %), 309 (M^+, 66), 266 (28), 253 (59), 119 (100), 106 (40).

4i: yellow crystals, m. p. 128~129℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.54~6.50 (m, 8H, Ar-H), 6.73 (s, 1H, =CH), 4.36 (s, 1H, NH), 4.12~3.88 (m, 1H, NCH), 2.12~0.84 (m, 10H, $(CH_2)_5$); IR (KBr, cm^{-1}), 3309 (N-H), 1703 (C=O), 1654 (C=C), 1573 (C=N), 1236; MS (m/z, %), 335 (M^+, 40), 253 (100), 119 (86), 106 (20).

4j: yellow crystals, m. p. 171~173℃, ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.50~6.51 (m, 13H, Ar-H), 6.78 (s, 1H, =CH), 4.73 (s, 3H, NH and NCH_2); IR (KBr, cm^{-1}), 3366 (N-H), 1707 (C=O), 1653 (C=C), 1577 (C=N), 1234; MS (m/z, %), 343 (M^+, 81), 314 (27), 223 (33), 167 (77), 106 (78), 91 (100).

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