A New Solution-phase Parallel Synthesis of 2-Alkylamino-3-aryl-5-phenylmethylene-3,5-dihydro-4*H*-imidazol-4-ones

DING, Ming-Wu(丁明武) **SUN, Yong**(孙勇) **LIU, Xiao-Peng**(刘小鹏) **LIU, Zhao-Jie***(刘钊杰)
Institute of Organic Synthesis, Central China Normal University, Wuhan, Hubei 430079, China

Thirteen new 2-alkylaminoimidazolones (4) were rapidly synthesized by a new solution-phase parallel synthetic method, which includes aza-Wittig reaction of iminophosphorane (1) with aromatic isocyanate to give carbodi-imide (2) and subsequent reaction of 2 with various aliphatic primary amine in a parallel fashion. The products were confirmed by ^{1}H NMR, MS, IR and X-ray crystallographic analysis. The unusual selectivity of the cyclization was probably due to the geometry of the guanidine intermediate.

Keywords solution-phase parallel synthesis, 2-alkylamino-3-aryl-5-phenylmethylene-3,5-dihydro-4*H*-imidazol-4-ones, aza-Wittig reaction

Introduction

Imidazolones are important heterocycles bearing fungicidal, *anti*-inflammotory and angiotensin II antagonistical activities.[1-4] Some of 2-alkylaminoimidazolones exhibit good antibacterial activities,[5] whereas others show potential antiviral and antitumor activities.[6] Until now, many of the new derivatives of imidazolones have been synthesized to evaluate their biological and pharmaceutical activities.

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. Solution-phase synthetic techniques no limitation of the scale is the advantage of which can be easily manipulated as well, but purification of the reaction products is difficult.

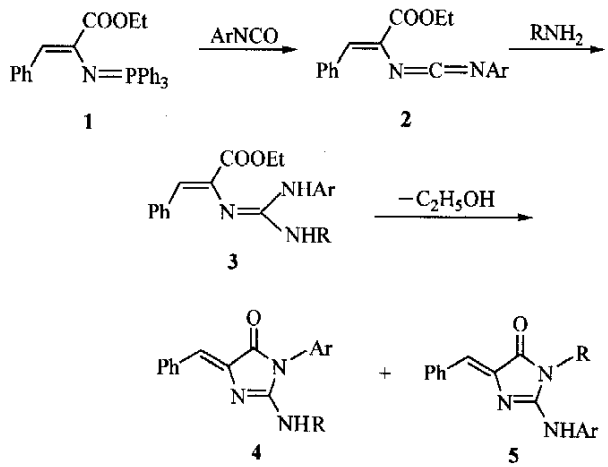
In our study on synthesis of biologically active imidazolones, a facile and selective synthesis of 2-alkylaminoimidazolones was developed.[9] Here we wish to report a new solution-phase parallel synthesis of some new derivatives of 2-alkylaminoimidazolones (**4**) (Scheme 1). By using this parallel synthetic method, **4** was obtained with unusual selectivity and the separation of **4** from the reaction mixture was easily carried out by simple recrystallization.

Results and discussion

The vinyliminophosphorane (**1**) reacted with aromatic isocyanates to give carbodi-imide (**2**). After removing the by-product Ph_3PO by recrystallization, the solution of **2** was divided equivalently into several parts to which were added various aliphatic primary amines separately. Pure **4** was obtained separately from the reaction mixture by recrystallization; isomers **5** were found to exist in minor amount by GC-MS detection. The structure of imidazolones (**4**) is deduced from their ^{1}H NMR data. For example, the ^{1}H NMR spectral data in **4b** showed the signals of NH at δ 4.48 as a wide absorption and NCH_2 at δ 3.60—3.55 as multiple absorption, which strongly suggested the existence of $NHCH_2CH_2CH_2CH_3$ group in **4b**. Moreover, when the sample was treated with deuterated water, the ^{1}H NMR spectrum data in **4b** showed the absorption of NCH_2 at δ 3.57 as triple peaks with the disappearance of signals of NH absorption. Whenever the primary amine used is small (R = *n*-Pr) or bulky (R = *t*-Bu), the cyclization was achieved all in moderate to good yields with the same selectivity. It is noteworthy that the isolated yield of **4** was higher when R becomes bulkier. The results are listed in Table 1.

In order to determine the configuration of **4**, **4b** was selected to analyze its ^{13}C NMR spectrum. The ^{13}C NMR spectrum of **4b** provided quaternary carbonyl carbon signals at δ

Scheme 1



* E-mail: ding5229@yahoo.com.cn
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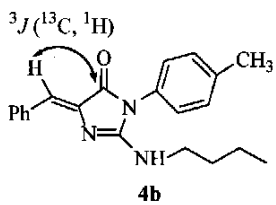
169.3 in double absorption. The coupling constant was 5.8 Hz and it was due to ^3J (^{13}C, ^1H) between the carbonyl carbon and the olefinic hydrogen ($^1H—C=C—^{13}C=O$). It was reported in the literature that the ^3J (^{13}C, ^1H) of some analogues of 5-arylmethyleneimidazolone (^3J of *Z*-form was in the range of 3—6 Hz whereas ^3J of *E*-form was in the range of 8—11 Hz).[10,11] So the configuration of **4b** was determined as in *Z*-form (Scheme 2).

Table 1 Preparation of 2-alkylaminoimidazolones (**4**)

Compound	Ar	R	Condition	Yield[a] (%)
4a	4-MePh	*n*-C_3H_7	r.t./3 h	61
4b	4-MePh	*n*-C_4H_9	r.t./3 h	56
4c	4-MePh	*n*-C_5H_{11}	r.t./3 h	68
4d	4-MePh	*i*-C_3H_7	r.t./5 h	80
4e	4-MePh	*t*-C_4H_9	r.t./7 h	82
4f	4-MePh	cyclohexyl	r.t./6 h	75
4g	4-MePh	$PhCH_2$	r.t./6 h	71
4h	3-ClPh	*n*-C_3H_7	r.t./4 h	54
4i	3-ClPh	*n*-C_4H_9	r.t./4 h	62
4j	3-ClPh	*n*-C_5H_{11}	r.t./4 h	58
4k	3-ClPh	*i*-C_3H_7	r.t./6 h	78
4l	3-ClPh	*t*-C_4H_9	r.t./10 h	83
4m	3-ClPh	cyclohexyl	r.t./6 h	70

[a] Isolated yields based on iminophosphorane (**1**).

Scheme 2



4b

The structure of **4** was further confirmed by X-ray crystallographic analysis. A single crystal of **4i** was obtained by slow evaporation from a methylene dichloride-petroleum ether b.p. 60—90 ℃ solution. X-Ray structure analysis showed that it is 2-butylamino substituted and the configuration of **4i** is in *Z*-form (Fig. 1). The selected bond lengths and angles for **4i** are listed in Table 2.

The formation of **4** (Scheme 3) can be rationalized in terms of an initial nucleophilic addition to give the guanidine intermediate **3** which cyclized to give **4** across the arylamine group rather than the alkylamine one. This will probably due to the geometry of the intermediate **3** which might be *Z*-form suitable for arylamine group to cyclize. It is guessed that the configurations of carbodi-imde **2** are mainly coplanar **2a** and **2b** due to the resonance effect. When the aliphatic primary amines react with **2a**, *Z*-**3a** will be formed for the amine will attack **2a** mainly from the down direction due to the steric hindrance of COOEt group. When the amines react with **2b**, *Z*-**3b** will be formed for the amine will attack **2b** mainly from the right direction due to the steric hindrance of pheny group.

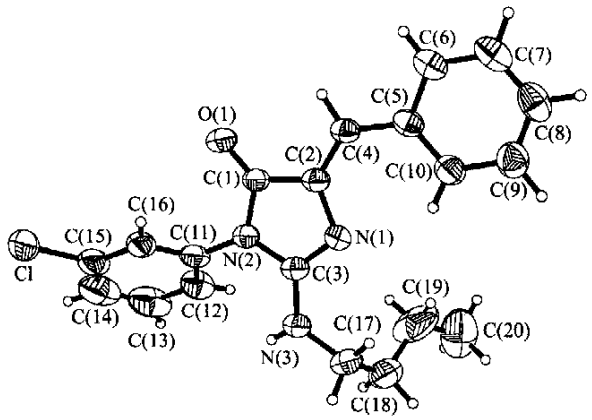
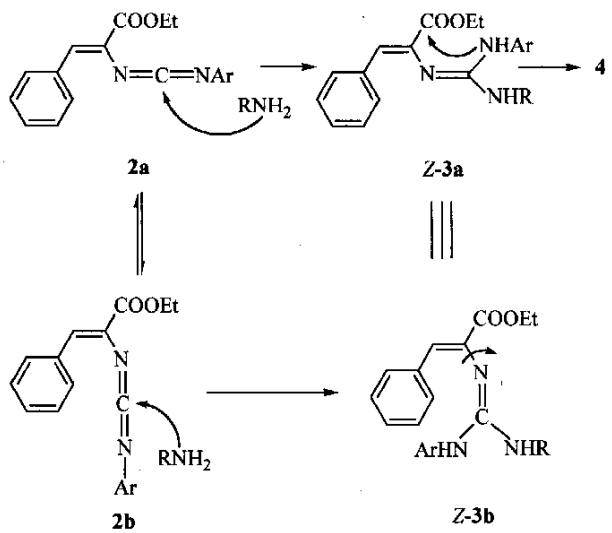


Fig. 1 Crystal structure of **4i**.

Table 2 Selected bond lengths (nm) and angles (°) for **4i**

Cl—C(15)	0.1727(6)	C(3)-N(1)-C(2)	105.7(3)
O(1)—C(1)	0.1219(4)	C(1)-N(2)-C(3)	106.3(3)
N(1)—C(3)	0.1297(4)	C(1)-N(2)-C(11)	125.3(3)
N(1)—C(2)	0.1399(4)	C(3)-N(3)-C(17)	122.4(3)
N(2)—C(1)	0.1389(4)	O(1)-C(1)-N(2)	124.9(3)
N(2)—C(3)	0.1404(4)	N(2)-C(1)-C(2)	104.4(3)
N(2)—C(11)	0.1404(4)	C(4)-C(2)-N(1)	127.5(3)
N(3)—C(3)	0.1427(4)	N(1)-C(2)-C(1)	109.3(3)
N(3)—C(17)	0.1446(4)	N(1)-C(3)-N(2)	114.3(3)
C(1)—C(2)	0.1461(5)	C(2)-C(4)-C(5)	129.2(3)
C(2)—C(4)	0.1342(4)	C(2)-C(4)-H(4)	116.9(17)

Scheme 3



Actually *Z*-**3a** is equivalent to *Z*-**3b** through the C—N single bond rotation.

In summary, the above solution-phase parallel synthetic method provides a high-speed and selective synthesis of 2-alkylaminoimidazolones. Due to the easily accessible and versatile starting material, this method has the potential in syn-

thesis of many biologically and pharmaceutically active imidazolone derivatives.

Experimental

Melting points were uncorrected. Mass spectra were measured on an HP5988A spectrometer. IR spectra were recorded on a PE-983 infrared spectrometer. NMR spectra were taken on a Varian Mercury 400 or 200 spectrometer. Elementary analysis was taken on a CHN 2400 elementary analysis instrument. X-Ray crystallographic analysis was made on a Bruker Smart-1000 CCD diffractometer with graphite monochromated Mo Kα ($\lambda = 0.071073$ nm) radiation. Iminophosphorane (**1**) was prepared by the reported method.[12]

Preparation of 2-alkylamino-3-(p-methylphenyl)-5-phenylmethylene-3,5-dihydro-4H-imidazol-4-ones (**4a—4g**)

To a solution of vinyliminophosphorane (**1**) (9.47 g, 21 mmol) in dry methylene dichloride (70 mL) was added 4-methylphenyl isocyanate (2.79 g, 21 mmol) under nitrogen at room temperature. After the reaction mixture was stood for 8 h, the solvent was removed off under reduced pressure and the mixture solvent of ether/petroleum ether (b. p. 30—60 ℃) (1:2, *V*:*V*, 140 mL) was added to precipitate triphenylphosphine oxide. After the mixture was filtered, the filtrate was condensed and methylene dichloride was added to make a solution of carbodi-imide (**2**) (70 mL), which was divided into seven parts (10 mL every part). To each part of **2** prepared above (10 mL) was added separately *n*-propyl amine (0.25 mL, 3 mmol), or *n*-butylamine (0.30 mL, 3 mmol), or *n*-pentylamine (0.35 mL, 3 mmol), or *iso*-propylamine (0.26 mL, 3 mmol), or *t*-butylamine (0.31 mL, 3 mmol), or cyclohexylamine (0.34 mL, 3 mmol), or benzylamine (0.33 mL, 3 mmol). After the reaction mixture was stood for 3—10 h, the solvent was removed off under reduced pressure and the residual was recrystallized from methylene dichloride/petroleum ether (30—60 ℃) to give 2-alkylamino-3-(*p*-methylpheny)-5-phenylmethylene-3, 5-dihydro-4*H*-imidazol-4-ones (**4a—4g**) separately.

4a Yellow crystals, m.p. 151—153 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15—7.16 (m, 9H, ArH), 6.77 (s, 1H, = CH), 4.52 (s, 1H, NH), 3.60—3.52 (m, 2H, NCH_2), 2.41 (s, 3H, $PhCH_3$), 1.73—0.92 (m, 5H, CH_2CH_3); IR (KBr) ν: 3354, 1716, 1657, 1587, 1376 cm^{-1}; MS (70 eV) *m/z* (%): 319 (M^+, 37), 277 (45), 133 (100), 116 (51). Anal. calcd for $C_{20}H_{21}N_3O$: C 75.21, H 6.63, N 13.16; found C 75.48, H 6.46, N 13.05.

4b Yellow crystals, m.p. 143—145 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15—7.16 (m, 9H, ArH), 6.78 (s, 1H, = CH), 4.48 (s, 1H, NH), 3.60—3.55 (m, 2H, NCH_2), 2.42 (s, 3H, $PhCH_3$), 1.66—0.95 (m, 7H, $CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ: 169.3 (C=O), 156.4 (C_2), 139.2, 135.8, 130.7, 130.6, 129.0, 128.4, 127.9, 127.1, 116.4 (ArC), 42.1 ($NHCH_2$), 32.0, 21.9, 20.7, 14.5 ($CH_2CH_2CH_3$ and $PhCH_3$); IR (KBr) ν: 3348, 1718, 1657, 1584, 1377 cm^{-1}; MS (70 eV) *m/z* (%): 333 (M^+, 24), 290 (11), 277 (30), 133 (100), 105 (75). Anal. calcd for $C_{21}H_{23}N_3O$: C 75.65, H 6.95, N 12.60; found C 75.74, H 6.83, N 12.82.

4c Yellow crystals, m.p. 133—134 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.14—7.17 (m, 9H, ArH), 6.79 (s, 1H, = CH), 4.49 (s, 1H, NH), 3.58—3.53 (m, 2H, NCH_2), 2.42 (s, 3H, $PhCH_3$), 1.68—0.90 (m, 9H, $(CH_2)_3CH_3$); IR (KBr) ν: 3361, 1715, 1657, 1586, 1376 cm^{-1}; MS (70 eV) *m/z* (%): 347 (M^+, 25), 290 (14), 277 (45), 133 (100), 105 (76). Anal. calcd for $C_{22}H_{25}N_3O$: C 76.05, H 7.25, N 12.09; found C 76.27, H 7.16, N 12.13.

4d Yellow crystals, m.p. 156—157 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15—7.16 (m, 9H, ArH), 6.78 (s, 1H, = CH), 4.42—4.35 (m, 1H, NCH), 4.29 (s, 1H, NH), 2.42 (s, 3H, $PhCH_3$), 1.29 (d, J = 6.2 Hz, 6H, $C(CH_3)_2$); IR (KBr) ν: 3281, 1714, 1654, 1580, 1376 cm^{-1}; MS (70 eV) *m/z* (%): 319 (M^+, 20), 277 (20), 133 (100), 116 (37). Anal. calcd for $C_{22}H_{25}N_3O$: C 75.21, H 6.63, N 13.16; found C 75.37, H 6.48, N 13.25.

4e Yellow crystals, m.p. 181—183 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.14—7.16 (m, 9H, ArH), 6.78 (s, 1H, = CH), 4.30 (s, 1H, NH), 2.42 (s, 3H, $PhCH_3$), 1.52 (s, 9H, $C(CH_3)_3$); IR (KBr) ν: 3314, 1713, 1655, 1581, 1377 cm^{-1}; MS (70 eV) *m/z* (%): 333 (M^+, 14), 277 (45), 133 (100), 116 (40). Anal. calcd for $C_{21}H_{23}N_3O$: C 75.65, H 6.95, N 12.60; found C 75.43, H 6.86, N 12.77.

4f Yellow crystals, m.p. 152—153 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.13—7.17 (m, 9H, ArH), 6.77 (s, 1H, = CH), 4.40 (d, J = 7.7 Hz, 1H, NH), 4.10—4.00 (m, 1H, NCH), 2.42 (s, 3H, $PhCH_3$), 2.13—1.16 (m, 10H, $(CH_2)_5$); IR (KBr) ν: 3270, 1712, 1652, 1582, 1376 cm^{-1}; MS (70 eV) *m/z* (%): 359 (M^+, 30), 277 (90), 133 (100), 116 (77). Anal. calcd for $C_{23}H_{25}N_3O$: C 76.85, H 7.01, N 11.69; found C 76.59, H 7.26, N 11.51.

4g Yellow crystals, m.p. 169—170 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.17—7.17 (m, 14H, ArH), 6.84 (s, 1H, = CH), 4.78 (s, 3H, NH and NCH_2), 2.39 (s, 3H, $PhCH_3$); IR (KBr) ν: 3367, 1711, 1658, 1580, 1369 cm^{-1}; MS (70 eV) *m/z* (%): 367 (M^+, 12), 181 (13), 116 (19), 91 (100). Anal. calcd for $C_{24}H_{21}N_3O$: C 78.45, H 5.76, N 11.44; found C 78.64, H 5.88, N 11.26.

Preparation of 2-alkylamino-3-(m-chlorophenyl)-5-phenylmethylene-3,5-dihydro-4H-imidazol-4-ones (**4h—4m**)

To a solution of vinyliminophosphorane (**1**) (8.12 g, 18 mmol) in dry methylene dichloride (60 mL) was added 3-chlorophenyl isocyanate (2.76 g, 18 mmol) under nitrogen at

room temperature. After the reaction mixture was stood for 4 h, the solvent was removed off under reduced pressure and ether/petroleum ether (b.p. 30—60 ℃) (1:2, *V*:*V*, 120 mL) was added to precipitate triphenylphosphine oxide. After the mixture was filtered, the filtrate was condensed and methylene dichloride was added to make a solution of carbodiimide (**2**) (60 mL), which was divided into six parts (10 mL every part). To each part of **2** prepared above (10 mL) was added separately *n*-propyl amine (0.25 mL, 3 mmol), or *n*-butylamine (0.30 mL, 3 mmol), or *n*-pentylamine (0.35 mL, 3 mmol), or *iso*-propylamine (0.26 mL, 3 mmol), or *t*-butylamine (0.31 mL, 3 mmol), or cyclohexylamine (0.34 mL, 3 mmol). After the reaction mixture was stood for 4—10 h, the solvent was removed off under reduced pressure and the residual was recrystallized from methylene dichloride/petroleum ether (b.p. 30—60 ℃) to give 2-alkylamino-3-(*m*-chlorophenyl)-5-phenylmethylene-3,5-dihydro-4*H*-imidazol-4-ones (**4h—4m**) separately.

4h Yellow crystals, m.p. 146—147 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.14—7.21 (m, 9H, ArH), 6.80 (s, 1H, =CH), 4.47 (s, 1H, NH), 3.60—3.55 (m, 2H, NCH_2), 1.70—0.98 (m, 5H, CH_2CH_3); IR (KBr) ν: 3356, 1715, 1657, 1588, 1371 cm^{-1}; MS (70 eV) *m*/*z* (%): 339 (M^+, 22), 341 (7), 297 (33), 153 (100), 116 (75). Anal. calcd for $C_{19}H_{18}ClN_3O$: C 67.16, H 5.34, N 12.37; found C 67.04, H 5.37, N 12.42.

4i Yellow crystals, m.p. 137—139 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.14—7.20 (m, 9H, ArH), 6.80 (s, 1H, =CH), 4.48 (s, 1H, NH), 3.61—3.56 (m, 2H, NCH_2), 1.69—0.96 (m, 7H, $CH_2CH_2CH_3$); IR (KBr) ν: 3358, 1718, 1658, 1589, 1370 cm^{-1}; MS (70 eV) *m*/*z* (%): 353 (M^+, 22), 355 (8), 310 (22), 297 (32), 153 (94), 116 (100). Anal. calcd for $C_{20}H_{20}ClN_3O$: C 67.89, H 5.70, N 11.88; found C 67.63, H 5.53, N 11.95.

4j Yellow crystals, m.p. 141—143 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15—7.19 (m, 9H, ArH), 6.79 (s, 1H, =CH), 4.48 (s, 1H, NH), 3.61—3.56 (m, 2H, NCH_2), 1.68—0.94 (m, 9H, $(CH_2)_3CH_3$); IR (KBr) ν: 3359, 1719, 1657, 1586, 1370 cm^{-1}; MS (70 eV) *m*/*z* (%): 367 (M^+, 17), 369 (6), 297 (10), 153 (100), 116 (68). Anal. calcd for $C_{21}H_{22}ClN_3O$: C 68.56, H 6.03, N 11.42; found C 68.63, H 6.17, N 11.22.

4k Yellow crystals, m.p. 126—128 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.17—7.18 (m, 9H, ArH), 6.80 (s, 1H, =CH), 4.44—4.37 (m, 1H, NCH), 4.31 (s, 1H, NH), 1.30 (d, 6H, J = 6.4 Hz, $C(CH_3)_2$); IR (KBr) ν: 3291, 1711, 1653, 1586, 1374 cm^{-1}; MS (70 eV) *m*/*z* (%): 339 (M^+, 27), 341 (9), 297 (26), 153 (100), 116 (74). Anal. calcd for $C_{19}H_{18}ClN_3O$: C 67.16, H 5.34, N 12.37; found C 67.25, H 5.41, N 12.23.

4l Yellow crystals, m.p. 155—156 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15—7.19 (m, 9H, ArH), 6.79 (s, 1H, =CH), 4.29 (s, 1H, NH), 1.55 (s, 9H, $C(CH_3)_3$); IR (KBr) ν: 3300, 1714, 1655, 1580, 1375 cm^{-1}; MS (70 eV) *m*/*z* (%): 353 (M^+, 18), 355(6), 297 (64), 153 (100), 116 (70). Anal. calcd for $C_{20}H_{20}ClN_3O$: C 67.89, H 5.70, N 11.88; found C 67.63, H 5.84, N 11.94.

4m Yellow crystals, m.p. 163—164 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.13—7.19 (m, 9H, ArH), 6.79 (s, 1H, =CH), 4.33 (s, 1H, NH), 4.10—4.00 (m, 1H, NCH), 2.15—1.18 (m, 10H, $(CH_2)_5$); IR (KBr) ν: 3279, 1714, 1654, 1585, 1375 cm^{-1}; MS (70 eV) *m*/*z* (%): 379 (M^+, 8), 381 (3), 297 (54), 153 (100), 116 (65). Anal. calcd for $C_{22}H_{22}ClN_3O$: C 69.56, H 5.84, N 11.06; found C 69.39, H 5.67, N 11.21.

References

1 Lacroix, G.; Peignier, R.; Pepin, R.; Bascou, J. P.; Perez, J.; Schmitz, C. *US 6002016*, **1999** [*Chem. Abstr.* **2000**, *132*, 35698e].

2 Bhalla, M.; Naithani, P. K.; Bhalla, T. N.; Saxena, A. K.; Shanker, K. *J. Indian Chem. Soc.* **1992**, *69*, 594.

3 Okazaki, T.; Kikuchi, K.; Watanable, T.; Suga, A.; Shibasaki, M.; Fujimori, A.; Inagaki, O.; Yanagisawa, I. *Chem. Pharm. Bull.* **1998**, *46*, 777.

4 Cremer, G.; Muller, J. C. *US 5457112*, **1995** [*Chem. Abstr.* **1996**, *124*, 117321a].

5 Kiec-Kononowicz, K.; Szymanska, E.; Motyl, M.; Holzer, W.; Bialecka, A.; Kasprowicz, A. *Pharmazie* **1998**, *53*, 680.

6 Khodair, A. I.; Bertrand, P. *Tetrahedron* **1998**, *54*, 4859.

7 Flynn, D. L.; Crich, J. Z.; Derraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 4874.

8 Li, W. Z.; Yun, L. H. *Chin. J. Org. Chem.* **1998**, *18*, 403 (in Chinese).

9 Ding, M. W.; Xu, Z. F.; Liu, Z. J.; Wu, T. J. *Synth. Commun.* **2001**, *31*, 1053.

10 Schuisky, P.; Twistel, W.; Grivas, S. *Heterocycles* **1998**, *48*, 1431.

11 Kidwai, M.; Sapra, P.; Bhushan, K. R.; Misra, P. *Synthesis* **2001**, 1509.

12 Molina, P.; Tarraga, A.; Lidon, M. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1727.

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