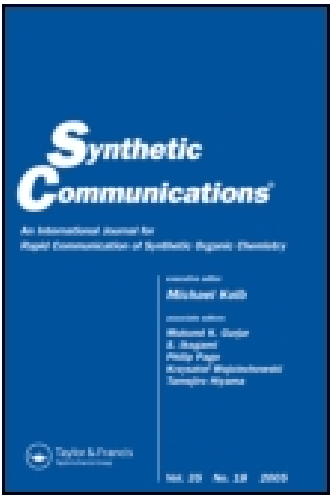


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A FACILE AND SELECTIVE SYNTHESIS OF 2-ALKYLAMINO-4H-IMIDAZOLIN-4-ONES

Ming-Wu Ding [a] , Zhi-Feng Xu [a] , Zhao-Jie Liu [a] & Tian-Jie Wu [a]
[a] Institute of Organic Synthesis, Central China Normal University , Wuhan, 430079, P.R. China
Published online: 09 Nov 2006.

To cite this article: Ming-Wu Ding , Zhi-Feng Xu , Zhao-Jie Liu & Tian-Jie Wu (2001) A FACILE AND SELECTIVE SYNTHESIS OF 2-ALKYLAMINO-4H-IMIDAZOLIN-4-ONES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:7, 1053-1057, DOI: 10.1081/SCC-100103536

To link to this article: http://dx.doi.org/10.1081/SCC-100103536

SYNTHETIC COMMUNICATIONS, 31(7), 1053–1057 (2001)

A FACILE AND SELECTIVE SYNTHESIS OF 2-ALKYLAMINO-4H-IMIDAZOLIN-4-ONES

Ming-Wu Ding,* Zhi-Feng Xu, Zhao-Jie Liu, and Tian-Jie Wu

Institute of Organic Synthesis, Central China Normal University, Wuhan, 430079, P.R. China

ABSTRACT

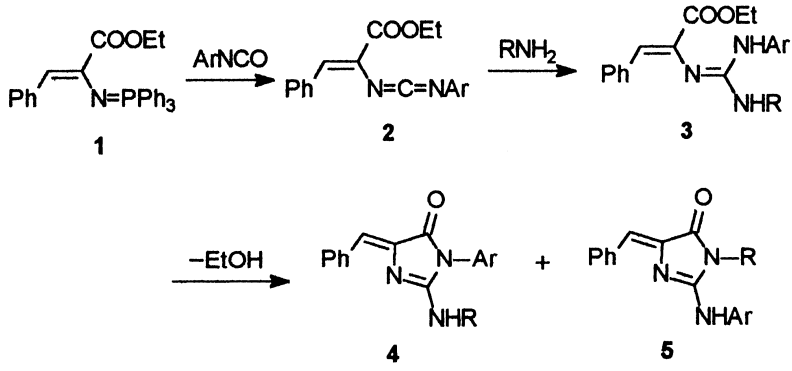
The carbodiimides **2**, obtained from aza-Wittig reactions of vinylimino-phosphorane **1** with aromatic isocyanates, reacted with aliphatic primary amines to give mainly 2-alkylamino-4H-imidazolin-4-ones **4** with unusual selectivity.

4H-Imidazolin-4-ones are important heterocycles having bactericidal, antiinflammatory, and angiotensin II antagonistical activities.[1–4] Some of them appear in a variety of biologically active molecules, particularly in some alkaloids in which a common structural unit is a derivatized 2-(alkyl)-amino-4H-imidazolin-4-one moiety.[5–7] Although there are many known methods for the synthesis of 4H-imidazolin-4-one,[8–12] the 2-alkylamino derivatives are not easily accessible by general routes. Here we report a facile and selective synthesis of 2-alkylamino-4H-imidazolin-4-ones via the reaction of aliphatic primary amines with functionalized carbodiimides under mild conditions.

The easily accessible vinyliminophosphorane **1**[13] reacted with aromatic isocyanates to give carbodiimides **2**, which were allowed to react

* Corresponding author.

with aliphatic primary amines to provide mainly imidazolinones **4**, one of the possible regioisomers. We obtained pure **4** from the reaction mixture by recrystallization but not **5**; however, **5** was found to exist in minor amount by GC-MS detection. The structure of imidazolinones **4** is mainly deduced from their ^{1}H NMR data. 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. The results are listed in Table 1.



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** across the arylamine group rather than the alkylamine one. This is probably due to the geometry of the intermediate **3**.

Table 1. Preparation of 2-Alkylamino-4H-imidazolin-4-ones 4

Compound	Ar	R	Condition	Yield (%)*
4a	Ph	*n*-C_3H_7	r.t./2 h	67
4b	Ph	*n*-C_4H_9	r.t./2 h	66
4c	Ph	*n*-C_5H_{11}	r.t./2 h	63
4d	Ph	*i*-C_3H_7	r.t./4 h	81
4e	Ph	*t*-C_4H_9	r.t./6 h	86
4f	4-Cl-Ph	*n*-C_3H_7	r.t./2 h	63
4g	4-Cl-Ph	*n*-C_4H_9	r.t./2 h	67
4h	4-Cl-Ph	*n*-C_5H_{11}	r.t./2 h	69
4i	4-Cl-Ph	*i*-C_3H_7	r.t./6 h	83
4j	4-Cl-Ph	*t*-C_4H_9	r.t./8 h	80

*Isolated yields based on iminophosphorane **1**.

EXPERIMENTAL

Melting points were uncorrected. MS were measured on a HP5988A spectrometer. IR were recorded on a Shimadzu IR-408 infrared spectrometer. NMR were taken on a Varian XL-200 spectrometer. Vinyliminophosphorane **1** was prepared by the literature report (13).

General Preparation of 2-Alkylamino-4H-imidazolin-4-ones 4

To a solution of vinyliminophosphorane **1** (2.26 g, 5 mmol) in dry methylene dichloride (15 mL) was added the aromatic isocyanate (5 mmol) under nitrogen at room temperature. After the reaction mixture was stirred for 2~4 h, the solvent was removed under reduced pressure and ether/petroleum ether (1:2, 20 mL) was added to precipitate the triphenylphosphine oxide. Filtered, the solvent was removed to give carbodiimide **2**, which was used directly without further purification.

To a solution of **2** prepared above in methylene dichloride (15 mL) was added the primary amine (5 mmol). After the reaction mixture was stirred for 2 h, the solvent was removed under reduced pressure and the residue was recrystallized from methylene dichloride/ether to give 2-alkylamino-4H-imidazolin-4-ones **4**.

4a: yellow crystals, m.p. 183°~184°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.16~7.10(m,10H,Ar-H), 6.70(s,1H, = CH), 4.58(t,1H,J = 5.4Hz,NH), 3.60~3.38(m,2H,NCH_2), 1.85~1.45(m,2H,CH_2), 0.94(t,3H,J = 7.2 Hz, cra = lCH_3); MS(*m*/*z*), 305(M^+,95%), 276(64%), 263(96%), 119(100%).

4b: yellow crystals, m.p. 174°~175°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.16~7.26(m,10H,Ar-H), 6.80(s,1H, = CH), 4.58(s,1H,NH), 3.59~3.53 (m,2H,NCH_2), 1.68~1.34(m,4H,CH_2CH_2), 0.97(t,3H,J = 7.2 Hz,CH_3); MS(*m*/*z*), 319(M^+,95%), 290(30%), 276(88%), 263(95%), 131(39%), 119(100%).

4c: yellow crystals, m.p. 172°~173°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.16~7.26(m,10H,Ar-H), 6.80(s,1H, = CH), 4.56(s,1H,NH), 3.62~3.52 (m,2H,NCH_2), 1.69~1.32(m,6H,$CH_2CH_2CH_2$), 0.92(t,3H,J = 6.7 Hz, CH_3); MS(*m*/*z*), 333(M^+,94%), 318(48%), 304(58%), 290(60%), 277(81%), 263(97%), 187(44%), 119(100%).

4d: yellow crystals, m.p. 122°~123°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.20~7.29(m,10H,Ar-H), 6.84(s,1H, = CH), 4.54~4.38(m,2H,NH and NCH), 1.34(d,6H,J = 6.2 Hz,$2CH_3$); MS(*m*/*z*),305(M^+,93%),290(36%),263 (90%),187(51%),119(100%).

4e: yellow crystals, m.p. 175°–176°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.18~7.26(m,10H,Ar-H), 6.79(s,1H, = CH), 4.36(s,1H,NH), 1.54(s,9H, $3CH_3$); MS(*m*/*z*), 319 (M^+,52%), 263(100%), 119(45%).

4f: yellow crystals, m.p. 156°~157°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.15~7.23(m,9H,Ar-H), 6.79(s,1H, = CH), 4.55(s,1H,NH), 3.60~3.50 (m,2H,NCH_2), 1.74~1.63(m,2H,CH_2), 0.99(t,3H,J = 7.3 Hz,CH_3);MS(m/z), 339(M^+,92%),310(49%),297(97%),153(100%),116(91%).

4g: light yellow crystals, m.p. 152°~153°C, ^{1}H NMR($CDCl_3$, 200 MHz) δ 8.15~7.22(m,9H,Ar-H), 6.78(s,1H, = CH), 4.54(s,1H,NH), 3.62~3.52(m,2H,NCH_2), 1.68~1.34(m,4H,CH_2CH_2),0.97(t,3H,J = 7.3 Hz, CH_3); MS(m/z),353(M^+,99%), 310(64%),297(100%),153(89%),116(95%).

4h: yellow crystals, m.p. 107°~108°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.15~7.22(m,9H,Ar-H), 6.80(s,1H, = CH),4.48(s,1H,NH),3.62~3.52 (m, 2H,NCH_2), 1.70~1.32(m,6H,$CH_2CH_2CH_2$), 0.92(t,3H,J = 7.0 Hz,CH_3); MS(m/z), 367(M^+,98%),310(38%), 297(100%)153(56%), 116(71%).

4i: yellow crystals, m.p. 60°~61°C, ^{1}H NMR($CDCl_3$,200 MHz) δ 8.20~7.25(m,9H,Ar-H), 6.82(s,1H, = CH), 452~4.36(m,2H,NH and NCH), 1.32(d,6H,J = 6.6 Hz,$2CH_3$); MS(m/z), 339(M^+,93%), 324(24%), 297(91%), 187(66%), 153(100%), 116(71%).

4j: light yellow crystals, m.p. 177°~178°C ^{1}H NMR($CDCl_3$,200 MHz) δ 8.21~7.26(m,9H,Ar-H), 6.81(s,1H, = CH), 4.34(s,1H,NH), 1.58(s,9H, $3CH_3$); MS(m/z), 353(M^+,38%), 297(100%), 153(34%), 116(18%).

ACKNOWLEDGMENTS

We gratefully acknowledge financial support of this work by the Dawn Plan of Science and Technology for Young Scientists of Wuhan City and Natural Science Foundation of Hubei Province.

REFERENCES

1. Kikuchi, K.; Watanable, T.; Okazaki, T.; Yanagisawa, I.; Inagaki, O. Japanese Patent 94279437.
2. Trivedi, B.; Shah, V.H. J. Indian Chem. Soc. **1993**, *70*, 645.
3. Bhalla, M.; Naithani, P.K.; Bhalla, T.N.; Saxena, A.K.; Shanker, K. J. Indian Chem. Soc. **1992**, *69*, 594.
4. Kumar, A.; Verma, M.; Saxena, A.K.; Shanker, K. Indian J. Chem., Sect B **1988**, *27B*, 301.
5. Guella, G.; Mancini, I.; Zibrowius, H.; Pietra, F. Helv. Chem. Acta. **1989**, *72*, 1444.
6. Debitus, C.; Cesario, M.; Guilhem, J.; Pascard, C.; Pais, M. Tetrahedron Lett. **1989**, *30*, 1535.

7. Chan, G.W.; Mong, S.; Hemling, M.E.; Freyer, A.J.; Offen, P.H.; DeBrosse, C.W.; Sarau, H.M.; Westley, J.W. J. Nat. Prod. **1993**, *56*, 116.
8. Ahluwailia, V.K.; Sharma, M.K.; Sharma, R. Org. Prep. Proced. Int. **1992**, *24*, 698.
9. Jain, A.; Mukerjee, A.K. Heterocycles **1987**, *26*, 1521.
10. Jain, A.; Mukerjee, A.K. J. Indian Chem. Soc. **1988**, *65*, 141.
11. Ding, M.W.; Xu, Z.F.; Wu, T.J. Synth. Commun. **1999**, *29*, 1171.
12. Ding, M.W.; Tu, H.Y.; Liu, Z.J.; Zhuang, N.B. Chem. J. Chinese Universities **1998**, *19*, 895.
13. Molina, P.; Tarraga, A.; Lidon, M.J. J. Chem. Soc., Perkin Trans. 1 **1990**, 1727.

Accepted May 8, 2000