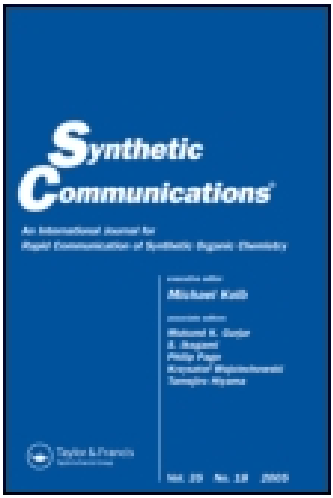

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Application of Carbodiimide in Heterocyclic Synthesis: New Facile Synthesis of 2-Aminoimidazolinone Derivatives

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APPLICATION OF CARBODIIMIDE IN HETEROCYCLIC SYNTHESIS: NEW FACILE SYNTHESIS OF 2-AMINOIMIDAZOLINONE DERIVATIVES

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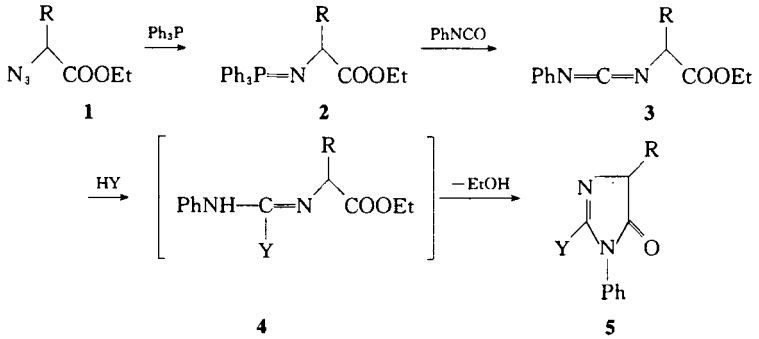
Abstract: A new facile synthesis of 2-amino-4H-imidazolin-4-ones **5** by using carbodiimides **3** which were obtained from aza-Wittig reaction of iminophosphoranes **2** with isocyanate is described.

4H-Imidazolin-4-ones are important heterocycles bearing good biological activities. Some of them have shown high herbicidal activities, such as imazamethabez and imazethapyr. They are also involved in some alkloids[1]. There are many known methods for the synthesis of imidazolinones[2] including the intramolecular aza-Wittig reaction[3], however, 2-amino substituted imidazolinones were not easily accessible by currently existing routes. In our work searching for biologically active heterocycles[4], we developed a new facile synthetic method to 2-amino-4H-imidazolin-4-one derivatives by using carbodiimides as synthons which were obtained from aza-Wittig reactions of iminophosphoranes with phenyl isocyanate.

The easily accessible azides **1** reacted with triphenylphosphine to create the iminophosphoranes **2**, which were allowed to react with phenyl isocyanate to produce carbodiimide **3** via the intermolecular aza-Wittig reaction. Then a nucleophile was added to yield the imidazolinone **5** through the cy-

clization of **4**. This approach supplies an easily accessible route to 4H-imidazolin-4-ones with various substituents. The reaction can be carried out either by one-pot version from the azides 1 or by isolation of the carbodiimides **3**.



Although the carbodiimide has been widely used in heterocyclic synthesis[5], the stability of some carbodiimides is uncertained. In preparation of carbodiimides **3**, the reaction temperature must be maintained below 30℃ (the best temperature is 0℃) otherwise a deep dark solution will result. However, with the careful control of the reaction condition, **3** can be easily isolated in 75~80% yields and be stored for about a month in room temperature, which providing a versatile synthon for imidazolinones. Attempts to isolate the guanidine intermediate **4** were not successful probably due to the rapid cyclization under room temperature.

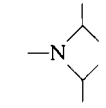
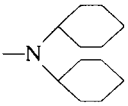
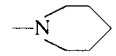
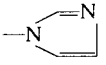
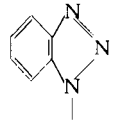
The reactivity of carbodiimide **3** to various nucleophiles was researched, the results are listed in Table 1 and summarized as follows:

1. When HY is a secondary amine ($HY=HNR^1R^2$), the carbodiimides **3** react smoothly with HY in room temperature to give imidazolinones **5**, however, when R^1, R^2 are bulky (R^1, $R^2=i$-Pr, c-hexyl), the reaction must be carried out in refluxing methylene dichloride, whereas when R^1, R^2 are aryl (R^1, R^2=Ph), the reaction didn't take place even after prolonged heating in methylene dichloride.

2. When HY is a heterocycles (HY=imidazole, benzotriazole), the reaction can take place in room temperature, however, the resulted imidazolinones **5** were unstable and getting dark when stored in room temperature.

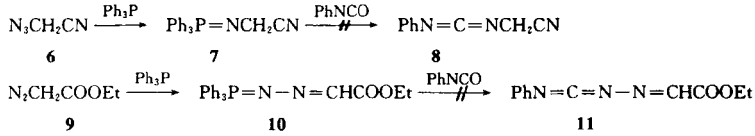
3. When HY is an alcohol (HY=MeOH, EtOH), only traces of products were detected and the carbodiimides **3** were recovered even after heating in CH_2Cl_2.

Table 1. Preparation of 4H-Imidazolin-5-one from the Carbodiimides 3

	R	Y	Reaction Temperature	Reaction Time	Yield(%)*
5a	H	$-NEt_2$	r.t.	2hr	85
5b	H		40 C	6hr	40
5c	H		40 C	8hr	45
5d	H	—N(Ph)Me	r.t.	4hr	63
5e	H		r.t.	2hr	78
5f	H		r.t.	2hr	80
5g	H		r.t.	2hr	75
5h	H		r.t.	2hr	75
5i	H	$-NPh_2$	40 C	18hr	0
5j	Me	$-NEt_2$	r.t.	2hr	86
5k	H	$-OCH_3$	40 C	5hr	trace
5l	H	—OEt	40 C	18hr	trace

* isolated yield based on carbodiimide 3.

Attempts to extend this method to prepare the carbodiimides **8** and **11**, which might be synthons for imidazoles or 1,2,4-triazin-5-ones, were unsuccessful. In these cases, the carbodiimides might produced but dimerization or polymerization might take place quickly[6].



EXPERIMENTAL

NMR were taken on a Varian XL-200 spectrometer. IR were recorded on a Shimadzu IR-408 infrared spectrometer. MS were measured on a HP 5988A spectrometer.

General procedure for the preparation of 4H-imidazolin-4-ones **5**:

A solution of triphenylphosphine (2.62 g, 10 mmol) in dry methylene dichloride (15 ml) was added dropwise under nitrogen at room temperature to a well-stirred solution of the azide **1** (10 mmol) in dry methylene dichloride (10 ml). The reaction mixture was stirred at room temperature for 0.5 h, then phenyl isocyanate (1.19 g, 10 mmol) was added at 0℃. After the reaction mixture was stirred at room temperature for 2 h, the solvent was removed off under reduced pressure and the residual material was eluted with ether/petroleum ether (1 : 10) through a short silica gel column to give the carbodiimde **3** (yields 75～80%).

A solution of the nucleophile HY (2 mmol) in CH_2Cl_2(5 ml) was added to **3** (2 mmol) in CH_2Cl_2(10 ml), the mixture was stirred for the time shown in Table 1 at room temperature or at refluxing temperature, the solvent was removed and the residual material was eluted with ethyl estate to give the imidazolinones.

^{1}HNMR, IR and MS for some compounds **5**:

5a: ^{1}HNMR ($CDCl_3$, 200MHz) δ 7.49～7.27 (m, 5H), 4.26(s, 2H), 3.04 (q, 4H, J=7.0Hz), 0.99(t,6H, J=7.0Hz). IR(cm^{-1}), 1740, 1620, 1440, 1275, 1100. MS(m/z), 231(M^+, 17.57%), 202(39.72%), 188 (11.83%), 145(42.71%), 112(51.13%), 77(100%).

5d: ^{1}HNMR ($CDCl_3$, 200MHz) δ7.44～6.64(m,10H), 4.28(s,2H), 3.22(s, 3H). IR(cm^{-1}), 1742, 1625, 1590, 1495. MS(m/z), 265(M^+, 10.15%), 131(10.43%), 77(100%).

5e: ^{1}HNMR($CDCl_3$, 200MHz)δ7.50～7.14(m,5H), 4.15(s,2H), 3.08～2.88 (m,4H), 1.64～1.32(m,6H). IR(cm^{-1}), 1738, 1624, 1420, 1338, 1280. MS(m/z), 243(M^+, 2.30%), 214(1.40%), 131(8.53%), 77(100%).

5f: ^{1}HNMR($CDCl_3$, 200MHz)δ7.50～7.12(m,5H), 4.14(s,2H), 3.60～3.44

(m,4H),3.05～2.90(m,4H). IR(cm^{-1}),1742,1620,1395,1114. MS(m/z),245(M^{+},6.58%),216(3.00%),188(15.13%),154(39.83),131(53.93),77(100%).

5j: ^{1}HNMR($CDCl_3$,200MHz)δ7.50～7.12(m,5H),4.14(q,1H,J=7.2Hz),2.97(q,4H,J=7.2Hz),1.42(d,3H,J=7.2Hz),0.94(t,6H,J=7.2Hz). IR(cm^{-1}),1740,1615,1495,1275,1180. MS(m/z),245(M^{+},5.04%),216(6.44%),145(15.56%),141(16.59%),119(19.84%),77(100%).

Acknowledgements

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