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# A Novel and Facile Carbodiimide-Mediated Synthesis of 2,3-Dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4(1*H*)-ones via a Tandem Intramolecular Nucleophilic Addition / Intramolecular Hetero Conjugate Addition Annulation Strategy

**Takao Saito* and Kensaku Tsuda**

Department of Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

**Abstract:** A novel and efficient carbodiimide-mediated synthetic method for new 2,3-dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4(1*H*)-ones (**4**) is described which involves initial intramolecular addition of an amino-nucleophile to the carbodiimide-cumulenic system, followed by intramolecular hetero conjugate addition annulation. Copyright © 1996 Elsevier Science Ltd

During the last past decade, potentially functionalized carbodiimides have found wide synthetic utility, especially in the field of heterocyclic chemistry.[1] The versatility of the carbodiimide-mediated synthesis of a wide range of nitrogen heterocycles has prompted us to develop a novel method for the synthesis of new heterocycles by utilizing these reactive species as the key intermediates. Recently we have demonstrated an efficient carbodiimide-mediated synthesis of dihydroquinazolines via a tandem strategy consisting of nucleophilic addition of an alcohol, an amine or a thiol, and subsequent intramolecular hetero conjugate addition of the pre-formed amine nucleophile.[2] Other related nucleophilic addition or substitution heterocyclizations ($A_N$, $S_N$) have also been reported.[3] Since sequential, intramolecular transformations often provide advantageous efficiency in organic synthesis,[4] we took interest in such strategy to apply it to the above process. We report here the first examples of an intramolecular-intramolecular mode of the tandem addition annulations on carbodiimides, which provide a facile and useful method for the synthesis of the otherwise hardly available, new 2,3-dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4(1*H*)-ones (**4**).[5,6]

In general, a critical point for intramolecular reactions is preparation of key intermediates (or sometimes their precursors) in the process. This is particularly true with such highly reactive species as **1** which should appropriately be built up with the components including the three diverse functional groups (N=C=N, NH and C=C-C=O) in a molecule. For the preparation of the carbodiimides **2** we took advantage of the aza-Wittig reaction of the iminophosphoranes **1** with isocyanates because isocyanate reacts chemoselectively on the ylide moiety under very mild conditions.[1] The requisite iminophosphorane **1** was prepared by the Staudinger reaction of the azide,[7] which was readily synthesized from *o*-toluidine via amination, azidation, and acylation.[8] The formed carbodiimides **2** smoothly underwent the intramolecular nucleophilic addition to give the dihydroquinazolines **3**, which, upon heating in a one-pot, were converted into the 2,3-dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4(1*H*)-ones **4** in fair to good overall yields.[6] It is noteworthy that the conversion **3** → **4** was efficiently accelerated by silica gel except for the case of **3f** → **4f**.[2] In this case the reluctance to cyclize can be attributed to the steric hindrance between the substituents (Me ($R^1$) and *c*-Hex ($R^2$)).

In summary, we have described the novel and efficient carbodiimide-mediated synthesis of 2,3-dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4(1*H*)-ones via the intramolecular tandem additions strategy. Conceptually, a

variety of pyrimidinone-fused heterocycles of type C in which a guanidine moiety constitutes the fusion joint, can be synthesized by this strategy. Further study on this subject is in progress in our laboratory.

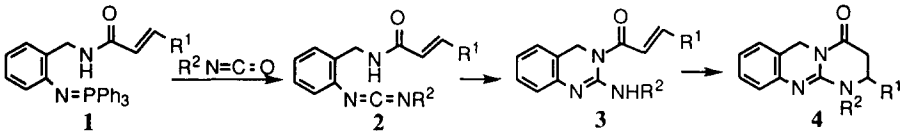
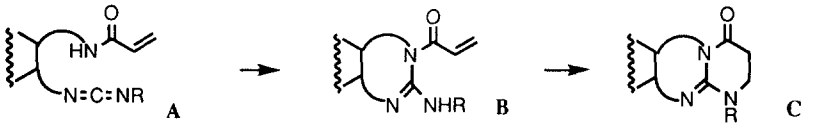


Table 1 Intramolecular Tandem Addition Reactions of Carbodiimides **2**

| Run | $R^1$ | $R^2$ | Temperature (Time / h) | Product (Yield / %) |
|---|---|---|---|---|
| **a** | H | Ph | r.t. (1) → 80 °C (1.5) | **4a** (65) |
| **b** | H | *p*-Tol | r.t. (1) → 80 °C (1.5) | **4b** (60) |
| **c** | H | *c*-Hex | 80 °C (3 + 2*) | **4c** (47) |
| **d** | Me | Ph | r.t. (3) → 80 °C (2*) | **4d** (69) |
| **e** | Me | *p*-Tol | r.t. (3) → 80 °C (2*) | **4e** (55) |
| **f** | Me | *c*-Hex | 80 °C (3 + 2*) | **3f** (47) |
| **g** | Me | Et | 60 °C (10) → 80 °C (2*) | **4g** (61) |
| **h** | Ph | Ph | 80 °C (1) | **4h** (95) |

* In the presence of silica gel.



**Typical Procedure** (Table 1, Run 1)

To a benzene solution (15 $cm^3$) of iminophosphorane **1a** (1.00 mmol, 436 mg) was added a benzene solution (15 $cm^3$) of phenyl isocyanate (1.10 mmol) at room temperature with stirring under an atmosphere of argon. After additional stirring for 1 h at r.t., the reaction mixture was then heated under reflux for 1.5 h. Evaporation of the solvent and column chromatography (silica gel, hexane-ethyl acetate 5:1 - 3:1) of the residue gave 1-phenyl-2,3-dihydro-6*H*-pyrimido[2,1-*b*]quinazolin-4(1*H*)-one (**4a**) in a 65 % yield as colorless crystals after recrystallization from $CH_2Cl_2$-diethyl ether.

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