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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

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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.

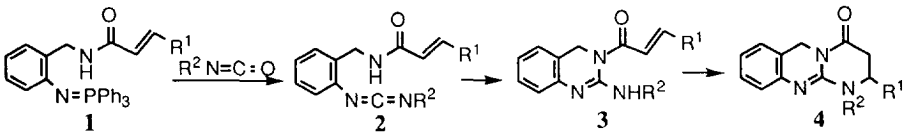
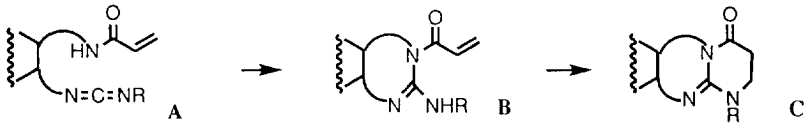


Table 1 Intramolecular Tandem Addition Reactions of Carbodiimides **2**

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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