

0040-4039(95)02130-2

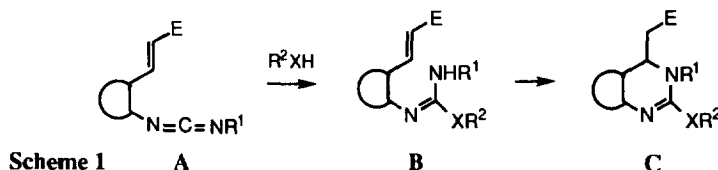
## A Facile and Efficient Carbodiimide-Mediated Synthesis of Dihydroquinazolines via a Tandem Nucleophilic Addition-Intramolecular Hetero Conjugate Addition Annulation Strategy

Takao Saito,\* Kensaku Tsuda and Yoji Saito

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

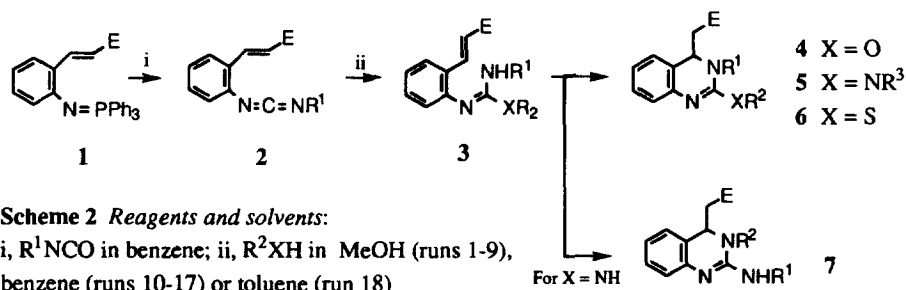
**Abstract:** A novel and efficient method is described for the synthesis of dihydroquinazoline derivatives which involves initial addition of a nucleophile (alcohol, amine and thiol) to the carbodiimide cumulenenic system followed by intramolecular hetero conjugate addition annulation.

The synthetic versatility of functionalized unsaturation-conjugated heterocumulenes has increasingly become apparent because of their rich chemistry, particularly in the field of heterocyclic chemistry.<sup>1</sup> The so-called tandem aza-Wittig reaction-conjugated carbodiimide-mediated electrocyclization methodology has successfully developed by Molina et al.<sup>2</sup> and by us.<sup>3,4</sup> Other related tandem carbodiimide-mediated annulations, *e.g.*, intramolecular  $A_N$  and  $S_N$ , and Diels-Alder reactions, have also been widely utilized in heterocyclic synthesis.<sup>3-5</sup> Thus, diverse ring-forming transformations by use of a heterocumulenic system incorporating an adjacent functional group can provide facile and efficient access to a wide variety of nitrogen-containing heterocycles.<sup>2-5</sup> In this context we have designed carbodiimides **A** bearing a Michael acceptor in a molecule which should take part in the ring formation to give a heterocycle **C** via intramolecular conjugate addition of **B** after addition of a nucleophile to one of the cumulene double bonds in **A**. We now report how readily and efficiently the dihydroquinazoline derivatives can be obtained by this strategy.



Carbodiimides **2** were prepared in good yields by the aza-Wittig reaction of iminophosphoranes with isocyanates.<sup>3-5</sup> The conversion **2** → **4a-e** was easily accomplished by simply heating **2** in methanol (Table 1, runs 1-5). The NaOMe-catalyzed reaction at room temperature was also found to be effective to afford **4e-h** in good yields. In either the catalyzed or uncatalyzed (thermal) reaction, the cyclohexyl substituent in  $R^1$  (runs 3 and 8) required longer reaction times than the other substituents, presumably due to the steric hindrance encountered in the cyclization step of **3**. With piperidine **2** ( $R^1 = \text{Ph}$ ) reacted readily at room temp. for 2 h to give **5a,c** in 93 and 97% yields, whilst the reaction of **2** ( $R^1 = \text{c-Hex}$ ,  $E = \text{CO}_2\text{Me}$ ) (run 11) was slow

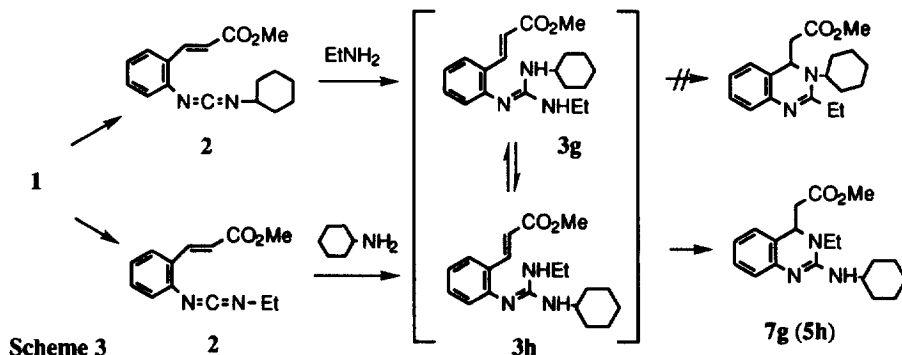
enough at the cyclization step (3 → 5) to obtain **3 b** (48%) along with **5 b** (40%) even after 30 h at 80 °C. It is now clear that compounds **3** are the key intermediates for the processes. In the presence of silica gel at 80 °C, the separated **3 b** was quantitatively converted to **5 b** within a few hours. It is significant that the cyclization step (3 → 5) was effectively accelerated by silica gel (see also runs 13 and 15-18). Treatment of **2** (R<sup>1</sup> = Ph) with butylamine afforded **5 e** (54%) and **7 e** (32%), whereas the reaction of **2** (R<sup>1</sup> = c-Hex) with the amine yielded **7 f** (98%) only. The selectivity in the latter results can be ascribed mainly to the large difference in cyclization rates due to the steric hindrance around the NHHex-c (R<sup>1</sup>) and NHBu-n (R<sup>2</sup>) groups. Indeed, this assumption is supported by the fact that the same products **7 g**(= **5 h**) are obtained exclusively in both reactions (Runs 16 and 17) which involve equilibrium between the configurationally flexible guanidines **3 g**



**Table 1** Reaction of Carbodiimides **2** with Nucleophiles

Run	E	R <sup>1</sup>	R <sup>2</sup>	X	Reaction conditions	Product (Yield, %)
1	CO <sub>2</sub> Me	Ph	Me	O	reflux / 3h	<b>4 a</b> (62)
2	CO <sub>2</sub> Me	p-Tol	Me	O	reflux / 3h	<b>4 b</b> (72)
3	CO <sub>2</sub> Me	c-Hex	Me	O	reflux / 40h	<b>4 c</b> (78)
4	CO <sub>2</sub> Me	Me	Me	O	reflux / 2h	<b>4 d</b> (62)
5	CN	Ph	Me	O	reflux / 5h	<b>4 e</b> (69)
6	CN	Ph	Me	O	r.t. / 5h / MeONa	<b>4 e</b> (68)
7	CN	p-Tol	Me	O	r.t. / 3h / MeONa	<b>4 f</b> (75)
8	CN	c-Hex	Me	O	r.t. / 72h / MeONa	<b>4 g</b> (76)
9	CN	Me	Me	O	r.t. / 6h / MeONa	<b>4 h</b> (98)
10	CO <sub>2</sub> Me	Ph	(CH <sub>2</sub> ) <sub>5</sub> N		r.t. / 2h	<b>5 a</b> (93)
11	CO <sub>2</sub> Me	c-Hex	(CH <sub>2</sub> ) <sub>5</sub> N		reflux / 30h	<b>3 b</b> (48) + <b>5 b</b> (40)
12	CN	Ph	(CH <sub>2</sub> ) <sub>5</sub> N		r.t. / 2h	<b>5 c</b> (97)
13	CN	c-Hex	(CH <sub>2</sub> ) <sub>5</sub> N		r.t. / 0.5h → reflux / 5h <sup>a</sup>	<b>5 d</b> (97)
14	CO <sub>2</sub> Me	Ph	n-Bu	NH	r.t. / 0.5h → reflux / 2h	<b>5 e</b> (54) + <b>7 e</b> (32)
15	CO <sub>2</sub> Me	c-Hex	n-Bu	NH	r.t. / 2h → reflux / 2h <sup>a</sup>	<b>7 f</b> (98)
16	CO <sub>2</sub> Me	c-Hex	Et	NH	r.t. / 14h → r.t. / 2h <sup>a</sup>	<b>7 g</b> (= <b>5 h</b> ) (96)
17	CO <sub>2</sub> Me	Et	c-Hex	NH	r.t. / 2.5h → r.t. / 2h <sup>a</sup>	<b>5 h</b> (= <b>7 g</b> ) (98)
18	CO <sub>2</sub> Me	Ph	p-Tol	S	reflux / 1h → r.t. / 1d <sup>a</sup>	<b>6 a</b> (70)

<sup>a</sup> Silica gel (ca. 1g) was added after completion of the initial addition step (2 → 3).



and **3h** as depicted in Scheme 3. Finally, a thiol was also found to play a role in the tandem carbodiimide-mediated nucleophilic addition-intramolecular hetero conjugate addition annulation to give **6a**.

In summary, the functionalized dihydroquinazoline compounds could readily and efficiently be synthesized via the tandem additions strategy. Further study on this subject is in progress in our laboratory.

#### Typical Procedure (Table 1, Run 11)

To a benzene solution ( $15 \text{ cm}^3$ ) of carbodiimide **2** (0.70 mmol, 198 mg) was dropwise added a benzene solution ( $15 \text{ cm}^3$ ) of piperidine (0.75 mmol) at room temperature with stirring under an atmosphere of argon. After additional stirring at r.t., the reaction mixture was then heated under reflux for 30 h. Evaporation of the solvent and column chromatography of the residue gave guanidine **3b** (48%) as an oil and dihydroquinazoline **5b** (40%) as pale brownish crystals (recrystallized from  $\text{CH}_2\text{Cl}_2$ -hexane).

**3b**:  $\delta_{\text{H}}$  0.86-1.30 (m, 8H), 1.50-1.64 (m, 7H), 1.83-1.88 (m, 2H), 3.19 (m, 5H), 3.77 (s, 3H), 6.43 (d, 1H, J 16.17 Hz), 6.79 (dd, 1H, J 7.26 and 0.99), 6.93 (ddd, 1H, J 7.26, 7.26 and 0.66 Hz), 7.24 (ddd, 1H, J 7.91, 7.26 and 1.32 Hz) and 7.52 (dd, 1H, J 7.91 and 1.32 Hz).

**5b**: mp. 128-129 °C; MS  $m/z$  369 ( $\text{M}^+$ , 40%) and 214 (100%);  $\delta_{\text{H}}$  1.06-1.32 (m, H), 1.54-1.89 (m, H), 2.34 (dd, 1H, J 14.18 and 5.27 Hz), 2.51 (dd, 1H, J 14.18 and 9.57 Hz), 3.17-3.71 (m, H), 3.65 (s, 3H), 4.70 (dd, 1H, J 9.57 and 5.27 Hz), 6.93 (ddd, 1H, J 7.26, 7.26 and 1.32 Hz), 7.01 (dd, 1H, J 7.26 and 1.32 Hz); 7.08 (dd, 1H, J 7.26 and 1.32 Hz) and 7.16 (ddd, 1H, J 7.26, 7.26 and 1.32 Hz).

**4a**: oil;  $m/z$  310 ( $\text{M}^+$ , 9%), 237 (100%); M,  $m/z$  310.1314.  $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_3$  requires M, 310.1318; IR 1740  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  2.70 (dd, 1H, J 14.84 and 7.59 Hz), 2.80 (dd, 1H, J 14.84 and 5.28 Hz), 3.52 (s, 3H), 3.87 (s, 3H), 5.26 (dd, 1H, J 7.59 and 5.28 Hz) and 6.97-7.39 (m, 9H);  $^{13}\text{C}$  NMR  $\delta$  40.63 ( $\text{CH}_2$ ), 51.70 ( $\text{CH}_3$ ), 54.34 ( $\text{CH}_3$ ), 60.07 (CH), 123.23 (CH)-170.69 (CO).

**6a**: oil; MS  $m/z$  402 ( $\text{M}^+$ , 15); HRMS  $m/z$  402.1409.  $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$  requires M, 402.1404; IR 1732  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  2.31 (s, 3H), 2.75 (d, 2H, J 6.93 Hz), 3.61 (s, 3H), 5.07 (t, 1H, J 6.93 Hz) and 6.95-7.28 (m, 13H).

**7f**: oil; MS  $m/z$  357 ( $\text{M}^+$ , 13); HRMS  $m/z$  357.2415.  $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_2$  requires M, 357.24183; IR 3424 and 1726  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  0.870 (t, 3H, J 7.26 Hz), 1.06-1.46 (m, 7H), 1.53 (ddt, 2H, J 7.26, 7.26 and 7.26 Hz), 1.59-1.76 (m, 3H), 2.04-2.08 (m, 3H), 2.44 (dd, 1H, J 14.85 and 6.59 Hz), 2.67 (dd, 1H, J 14.85 and 7.26 Hz), 3.14 (dt, 1H, J 14.52 and 7.26 Hz), 3.39 (dt, 1H, J 14.52 and 7.26 Hz), 3.64 (s, 3H), 4.82 (br. s, 1H), 4.66 (dd, 1H, J 7.26 and 6.59 Hz) and 6.83-7.19 (m, 4H).

## References and Notes

- (a) Moore, H. W.; Decker, O. H. W. *Chem. Rev.*, **1986**, 86, 821. (b) Snider, B. B. *Chem. Rev.*, **1988**, 88, 793. (c) Tsuge, O. *Heterocycles*, **1979**, 12, 212 and 1067. (d) Tsuge, O. Acyl and Thioacyl Derivatives of Isocyanates, Thiocyanates, and Isothiocyanates in *The Chemistry of Cyanates and Their Thio Derivatives*, Patai, S. Ed.; John Wiley & Sons, Inc.: New York, 1977; p. 445. (e) Arbuзов B. A.; Zobova, N. N. *Synthesis*, **1982**, 433. (f) Mukerjee, A. K.; Ashare, R. *Chem. Rev.*, **1991**, 91, 1. (g) Barker, M. W.; McHenry, W. E.; Wolman, Y.; Brown, R. F. C.; Eastwood, F. W. in *The Chemistry of Cyanates and Their Thio Derivatives*, Patai, S. Ed.; John Wiley & Sons, Inc.; New York, 1980; ch. 17-19. (h) Boger, D. L. *Tetrahedron*, **1983**, 39, 2869. (i) Dondoni, A. *Heterocycles*, **1980**, 14, 1547. (j) Aumann, R. *Angew. Chem. Int. Ed. Engl.*, **1988**, 27, 1456. (k) Williams, A.; Ibrahim, I. T. *Chem. Rev.*, **1981**, 81, 589; and references cited therein.
- (a) Molina, P.; Arques A.; Vinader, M. A. *J. Org. Chem.*, **1988**, 53, 4654. (b) Molina, P.; Arques, A.; Fresneda, P. M.; Vinader, M. A.; Foces-Foces, M. C. *Chem. Ber.*, **1989**, 122, 307. (c) Molina, P.; Vilaplana, M. J. *Synthesis*, **1990**, 474. (d) Molina, P.; Tarraga, A.; Lidon, M. J. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 1727. (e) Molina, P.; Arques, A.; Vinader, M. V. *J. Org. Chem.*, **1990**, 55, 4724.
- (a) Saito, T.; Nakane, M.; Endo, M.; Yamashita, H.; Oyamada, Y.; Motoki, S. *Chem. Lett.*, **1986**, 135. (b) Saito, T.; Ohmori, H.; Furuno, E.; Motoki, S. *J. Chem. Soc., Chem. Commun.*, **1992**, 22.
- For a review: (a) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.*, **1992**, 24, 209. (b) Barluenga, J.; Palacios, F. *Org. Prep. Proced. Int.*, **1991**, 23, 1. (c) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron*, **1992**, 48, 1353. (d) Gusar, N. I. *Russ. Chem. Rev.*, (Engl. Transl.), **1991**, 60, 146.
- (a) Saito, T.; Ohkubo, T.; Maruyama, K.; Kuboki, H.; Motoki, S. *Chem. Lett.*, **1993**, 1127. (b) Saito, T.; Ohmori, H.; Ohkubo, T.; Motoki, S. *J. Chem. Soc., Chem. Commun.*, **1993**, 1802. (c) Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron*, **1989**, 45, 4263. (d) Molina, P.; Fresneda, P. M.; Almendros, P. *Synthesis*, **1993**, 54. (e) Molina, P.; Arques, A.; Molina, A. *Synthesis*, **1991**, 21. (f) Molina, P.; Lorenzo, A.; Aller, E. *Synthesis*, **1992**, 297. (g) Molina, P.; Almendros, P.; Fresneda, P. M. *Tetrahedron Lett.*, **1994**, 35, 2235. (h) Molina, P.; Alajarin, M.; Vidal, A.; Sanchez-Andrada, P. *J. Org. Chem.*, **1992**, 57, 929. (i) Nitta, M.; Soeda, H.; Koyama, S.; Iino, Y. *Bull. Chem. Soc. Jpn.*, **1991**, 64, 1325. (j) Noguchi, M.; Onimura, K.; Isomura, Y.; Kajigaeshi, S. *J. Heterocyclic Chem.*, **1991**, 28, 885. (k) Okawa, T.; Eguchi, S. *Synlett*, **1994**, 555. (l) Wamhoff, H.; Wintersohl, H.; Stolben, S.; Paasch, J.; Nai-jue, Z.; Fang, G. *Liebigs Ann. Chem.*, **1990**, 901. (m) Wamhoff, H.; Schmidt, A. *J. Org. Chem.*, **1993**, 58, 6976. (n) Wamhoff, H.; Bamberg, C.; Herrmann, S.; Nieger, M. *J. Org. Chem.*, **1994**, 59, 3985. (o) Wamhoff, H.; Schmidt, A. *Heterocycles*, **1993**, 35, 1055. (p) Lee, K.-J.; Kang, S.-U. *Tetrahedron Lett.*, **1995**, 36, 2815. (q) Lee, K.-J.; Kim, S. H.; Kim, S.; Park, H.; Cho, Y. R.; Schweizer, E. E. *Synthesis*, **1994**, 1057.

(Received in Japan 26 September 1995; revised 4 November 1995; accepted 10 November 1995)