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SYNTHESIS OF 2,3,4-TRI-SUBSTITUTED 3,4-DIHYDRO-QUINAZOLINES *VIA* TANDEM NUCLEOPHILIC ADDITION/EPOXY RING-OPENING CYCLIZATION METHODOLOGY USING *N*-(2-OXIRANYLPHENYL)CARBODIIMIDES WITH NUCLEOPHILES[†]

Takao Saito,* Tatsuya Ote, Masahiro Shiotani, Hiroko Kataoka, Takashi Otani, and Noriki Kutsumura

Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan. tsaito@rs.kagu.tus.ac.jp

Abstract – *N*-(2-Oxiranylphenyl)carbodiimides, which were synthesized *via* an aza-Wittig reaction of the corresponding functionalized iminophosphoranes with aromatic and aliphatic isocyanates, underwent O-, S-, C-, or N-nucleophilic addition onto a cumulene, followed by an epoxy ring-opening cyclization with the newly formed NH-nucleophile in a one-pot reaction to furnish 2,3-disubstituted 4-(hydroxymethyl)-3,4-dihydroquinazolines in a highly stereospecific manner.

We have been interested in the chemistry of functionalized (conjugated) heterocumulenes such as carbodiimides, and their use as key substrates for the synthesis of nitrogen heterocycles.[1] Considerable advances in the chemistry have been made.[2] For examples, the synthetic approaches used included an aza-Wittig reaction of iminophosphoranes with isocyanates to generate functionalized carbodiimides, followed by the use of various ring-forming transformations such as (a) electrocyclization,[1a-c,3] (b) intra-[1b-d,4] or (c) intermolecular Diels-Alder type reaction,[1a,c,5] and (d, e) various types of cyclizations (various bond-forming reactions, *e.g.*, nucleophilic addition/substitution,[1e-g,3a,6] and Pauson-Khand reaction[1h-j,7]) in tandem with the heterocumulene functionality and adjacent available functional group, to furnish nitrogen heterocycles **A** (Chart 1). Our ongoing program to develop a useful synthetic method based on this concept of a functionalized carbodiimide-mediated, tandem annulation strategy for

[†]This paper is dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 85th birthday.

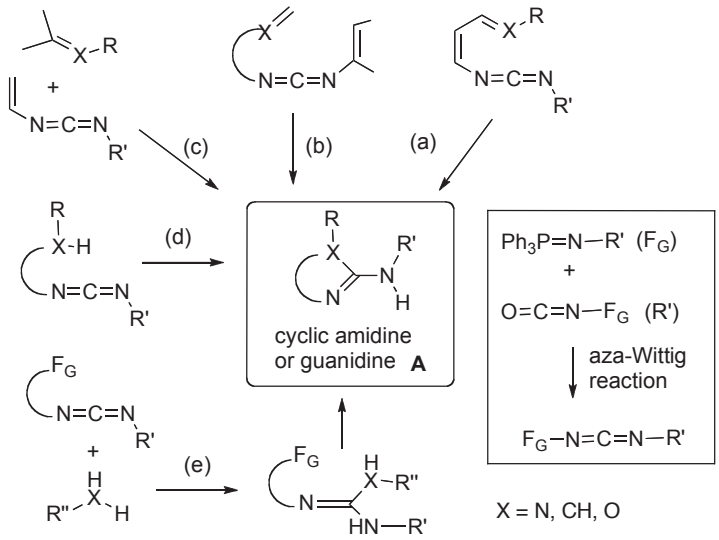
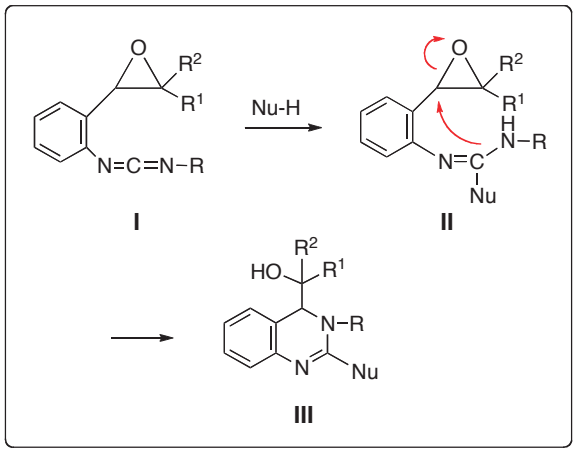


Chart 1 Various tandem cyclization pathways leading to cyclic amidines or guanidines

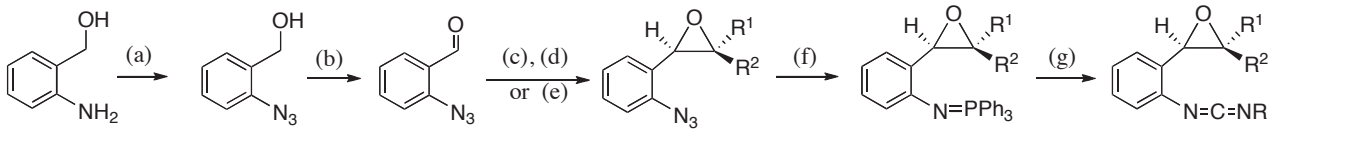


Scheme 1. Tandem nucleophilic addition /epoxy ring-opening cyclization

heterocyclic synthesis prompted us to seek a suitable new functional group that could play an important part in the ring-forming reaction in tandem.

Scheme 1 depicts our new strategy. A nucleophile initially adds to the cumulene carbon of the (2-oxyranylphenyl)carbodiimide **I** to give the intermediate **II**, the newly formed NH-nucleophilic center, which subsequently attacks the epoxy ring resulting in a ring-opening cyclization in a permitted 6-exo-tet manner to produce 4-(hydroxymethyl)dihydroquinazoline **III**. Herein, we report the results of this new synthetic approach to dihydroquinazolines having a β-amino-alcohol unit.

First, the key substrates **6**-**7**, epoxy-carbodiimides bearing a variety of substituents (R, R^1, R^2), were prepared from *o*-aminobenzyl alcohol (**1**) according to the route shown in Scheme 2.



6(*trans*): $R^1 = CO_2Et$, $R^2 = H$
7(*trans*): $R^1 = Ph$, $R^2 = H$
7(*cis*): $R^1 = H$, $R^2 = Ph$

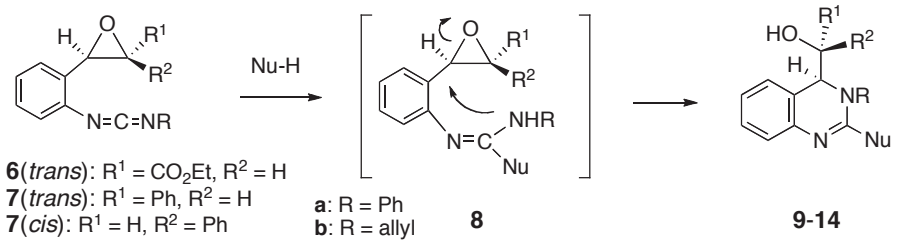
(a) i) $NaNO_2$/aq.HCl, 1 h; ii) NaN_3, 1 h/aq.HCl, 0 °C, 64%
(b) PCC, rt, 2 h/CH_2Cl_2, 94% (c) $ClCH_2CO_2Et$, Na/EtOH, rt, 4 h, 99%
(d) BnBr, tetrahydrothiophene, K_2CO_3/MeCN, rt, 3 d, 80% (e) i) $PhCH{=}PPh_3$, ii) *m*CPBA
(f) Ph_3P/CH_2Cl_2, 96% (g) R-NCO/CH_2Cl_2, 0 °C-rt, 1-4 h, 88-99%

Scheme 2. Preparation of the oxiranylcarbodiimides **6**-**7**

Oxiranylcarbodiimides **6**-**7** obtained in this way were allowed to react initially with alcohol nucleophiles; the results are summarized in Table 1. The reaction with methanol or *o*-chlorophenol in the presence of the corresponding sodium alcoholate or phenolate proceeded slowly to afford the dihydroquinazolines **9**

and **10**/**10'** in good to moderate yields (Table 1, runs 1–6).[8] The presence of the base is necessary because the reaction without the base did not proceed even at 110 °C for 10 h. We believe that the reaction is initiated by nucleophilic addition onto the cumulene bond to form the intermediate **8**, followed by the intramolecular nucleophilic attack at the proximal epoxy ring by the newly formed amine nucleophile, with simultaneous epoxy ring-opening to produce the dihydroquinazolines **9** and **10**/**10'**. The exclusive formation of the *erythro*-isomer from *trans*-**6**/**7** and *threo*-isomer from *cis*-**7** confirms that the

Table 1. Reaction of carbodiimides **6**-**7** with O-, S- and C-nucleophiles to give dihydroquinazolines **9**-**14**



6(*trans*): R^1 = CO_2Et, R^2 = H
7(*trans*): R^1 = Ph, R^2 = H
7(*cis*): R^1 = H, R^2 = Ph

a: R = Ph
b: R = allyl

8

9-14

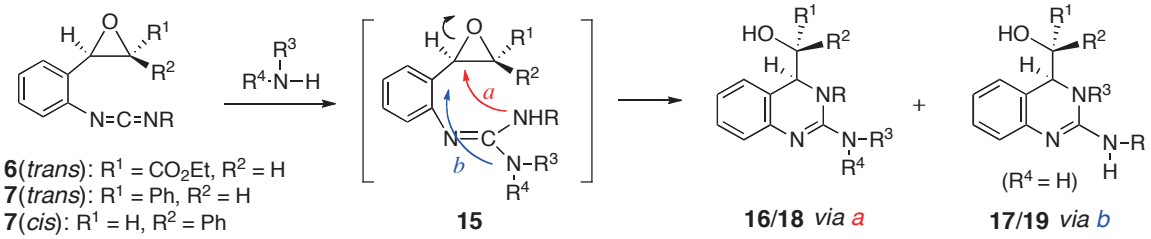
Run	Carbo-diimide	R^1	R^2	R	Nu-H	Base (equiv)	Reaction Conditions	Product[a] (Yield/%)
1	**6a**	CO_2Et	H	Ph	MeOH	MeONa (0.1)	rt, 3 d, CH_2Cl_2	**9a** (61)
2	**6b**	CO_2Et	H	allyl	MeOH	MeONa (0.2)	rt, 48 h, CH_2Cl_2	**9b** (37)
3	**6a**	CO_2Et	H	Ph	*o*-ClPhOH	Na (1.0)	rt, 2 h, CH_2Cl_2	**9c** (54)
4	**7a**	Ph	H	Ph	MeOH	MeONa (0.1)	0 °C→rt, 5 d, CH_2Cl_2	**10a** (66)
5	**7a**	Ph	H	Ph	*o*-ClPhOH	Na (1.0)	0 °C→rt, 5 d, CH_2Cl_2	**10b** (44)
6	**7a**(*cis*)	H	Ph	Ph	MeOH	MeONa (0.1)	0 °C→rt, 6 h, MeOH	**10'a** (85)
7	**6a**	CO_2Et	H	Ph	$C_{12}H_{25}SH$	Et_3N (1.0)	0 °C, 1 h, CH_2Cl_2	**11a** (82)
8	**6b**	CO_2Et	H	allyl	$C_{12}H_{25}SH$	Et_3N (1.0)	0 °C, 10 min, CH_2Cl_2	**11b** (67)
9	**6a**	CO_2Et	H	Ph	PhSH	-	0 °C, 10 min, CH_2Cl_2	**11c** (96)
10	**7a**	Ph	H	Ph	$C_{12}H_{25}SH$	Et_3N (1.0)	0 °C→rt, 1 h, CH_2Cl_2	**12a** (82)
11	**7a**	Ph	H	Ph	PhSH	-	0 °C→rt, 24 h, CH_2Cl_2	**12b** (85)
12	**7a**(*cis*)	H	Ph	Ph	$C_{12}H_{25}SH$	Et_3N (1.0)	0 °C→rt, 2 h, MeOH	**12'a** (90)
13	**6a**	CO_2Et	H	Ph	$NCCH_2CO_2Et$	NaH (1.0)	–78→–40 °C, 1 h, THF	**13a** (98)
14	**6a**	CO_2Et	H	Ph	$MeCOCH_2COMe$	NaH (1.0)	–78°C→rt, 2 h, THF	**13b** (60)
15	**7a**	Ph	H	Ph	$NCCH_2CO_2Et$	NaH (1.0)	–78→0 °C, 10 min, THF	**14a** (76)
16	**7a**(*cis*)	H	Ph	Ph	$NCCH_2CO_2Et$	NaH (1.0)	–78 °C →rt, 30 min, THF	**14'a** (89)

[a] A prime mark for the products **10'** and **12'** denotes *threo*-isomer. For the others (**9**-**12**), *erythro*-isomers.

intramolecular nucleophilic substitution in the epoxy ring-opening process proceeded with complete inversion of the stereogenic center at the epoxy-2-position. Similarly, the oxiranylcarbodiimides **6**-**7** also

reacted with dodecanethiol and benzenethiol to afford the dihydroquinazolines **11** and **12/12'** stereospecifically in good yields (runs 7–12).[8] It is noteworthy that the reaction with benzenethiol proceeded even in the absence of an amine base (Et_3N) (runs 9 and 11). The reaction with carbon nucleophiles was also examined. Treatment with Grignard reagents RMgBr (R = Me, *n*-Hex, Ph) or enolate anions derived from acetonitrile and acetophenone failed. However, reaction with stable enolate anions derived from 1,3-diketones successfully resulted in the formation of the expected C-attacking quinazoline products **13** and **14/14'** (runs 13–16).

Table 2. Reaction of carbodiimides **6**-**7** with N-nucleophiles to give dihydroquinazolines **16**-**19**



Run	Carbo-diimide	R^1	R^2	R	R^3 R^4N-H	Reaction Conditions	Product[a] (Yield/%)
1	**7a**(*cis*)	H	Ph	Ph	pyperidine	0 °C, 10 min, CH_2Cl_2	**16'a** (78)
2	**7b**	Ph	H	allyl	pyperidine	0 °C, 10 min, CH_2Cl_2	**16b** (33)[b]
3	**7c**	Ph	H	*p*-Tol	allylNH_2	0 °C, 1 h, CH_2Cl_2	**16c** (75)
4	**7d**	Ph	H	*p*-ClPh	allylNH_2	0 °C, 10 min, CH_2Cl_2	**16d** (66)
5	**7e**	Ph	H	*c*-Hex	allylNH_2	0 °C, 1 h, CH_2Cl_2	**17e** (42)[b]
6	**7f**	Ph	H	allyl	*c*-HexNH_2	0 °C, 1 h, CH_2Cl_2	**16f** [=**17e**] (64)
7	**7a**(*cis*)	H	Ph	Ph	allylNH_2	0 °C, 10 min, CH_2Cl_2	**16'g** (93)
8	**7e**(*cis*)	H	Ph	*c*-Hex	allylNH_2	rt, 2 h, CH_2Cl_2	**17'e** (99)
9	**7f**(*cis*)	H	Ph	allyl	*c*-HexNH_2	0 °C, 30 min, CH_2Cl_2	**16'f** [=**17'e**] (72)
10	**6a**	CO_2Et	H	Ph	allylNH_2	rt, 10 min, CH_2Cl_2	**18a** (99)
11	**6a**	CO_2Et	H	Ph	*c*-HexNH_2	rt, 30 min, CH_2Cl_2	**18b** (85)
12	**6b**	CO_2Et	H	allyl	$PhNH_2$	114 °C, 3 h, toluene	**19a** [=**18a**] (30)
13	**6b**	CO_2Et	H	allyl	*c*-HexNH_2	rt, 1 h, CH_2Cl_2	**18c** (45)
14	**6c**	CO_2Et	H	*c*-Hex	allylNH_2	rt, 3 h, CH_2Cl_2	**19c** [=**18c**] (60)
15	**6d**	CO_2Et	H	*p*-ClPh	allylNH_2	rt, 10 min, CH_2Cl_2	**18d** (80)

[a] A prime mark for the products **16'** and **17'** denotes *threo*-isomer. For the others (**16**-**19**), *erythro*-isomers.

[b] Yield for the reaction performed in one-pot from corresponding azide **4**.

The carbodiimides **7a**(*cis*) and **7b** reacted rapidly with a secondary amine, piperidine, at 0 °C for 10 min to give the corresponding dihydroquinazolines **16'a** and **16b**, respectively, in fairly good yield (Table 2,

runs 1–2). The reaction apparently proceeded through the guanidine intermediate **15**, in which an epoxy ring-opening cyclization *via* path "a" by NHR attack was involved. The reaction of carbodiimides **7c**, **7d** and **7a**(*cis*) (R = aryl) and **7f** and **7f**(*cis*) (R = allyl) with a primary amine (R^4 = H: allyl amine, cyclohexyl amine) also produced the corresponding quinazolines **16c**, **d**, **f** and **16'f**, **g** similarly *via* the path "a" in **15** with the ambidentate nucleophilic guanidines (runs 3, 4, 6, 7 and 9). In contrast, the reaction of carbodiimides **7e** and **7e**(*cis*) bearing a bulky substituent (R = cyclohexyl group) with a less bulky allyl amine yielded quinazolines **17e** and **17'e** *via* the alternative path "b" by NHR^3 attack in **15** (runs 5 and 8). Similarly, the reaction of *trans*-[(3-ethoxycarbonyloxyran-2-yl)phenyl]carbodiimides **6a**-**d** with a primary amine (allyl amine, cyclohexyl amine, aniline) resulted in the formation of quinazolines **18** or **19** (runs 10–15). The preferred formation of either **16**/**18** or **17**/**19**[9] may be ascribed principally to the steric hindrance of the NHR(R^3) group rather than to its nucleophilicity,[10] if the allyl group is relatively bulkier than a phenyl group under the conditions in **15**.

In summary, we have developed the functionalized carbodiimide-mediated tandem nucleophilic addition /epoxy ring-opening cyclization method for stereospecific synthesis of 2,3-disubstituted 4-(hydroxymethyl)-3,4-dihydroquinazolines.

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8. The structures **9**-**14** were determined spectroscopically. **12a** (Table 1, run 10)**:** Colorless oil; ^{1}H NMR ($CDCl_3$, 500.0 MHz) δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.25-1.35 (m, 18H), 1.56-1.63 (m, 2H), 2.44 (brs, 1H, OH), 2.93 (ddd, *J* = 6.9, 8.1, 12.9 Hz, 1H), 3.19 (ddd, *J* = 6.6, 8.1, 12.9 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H, H-4), 4.75 (d, *J* = 6.8 Hz, 1H, CH-O), 6.64-6.66 (m, 2H, Ar), 6.72 (d, *J* = 7.4 Hz, 1H, Ar), 6.99 (dt, *J* = 1.2, 7.4 Hz, 1H, Ar), 7.13-7.15 (m, 3H, Ar), 7.21 (d, *J* = 7.8 Hz, 1H, Ar), 7.26-7.35 (m, 6H, Ar). ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 14.1 (CH_3), 22.6 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 31.3 (CH_2), 31.8 (CH_2), 69.7 (CH, C-4), 74.2 (CH, C-O), 122.0 (C), 123.2 (CH, Ar), 123.8 (CH, Ar), 126.7 (CH, Ar), 127.0 (2CH, Ph), 127.1 (CH, Ar), 127.4 (2CH, Ph), 127.9 (CH, Ar), 128.2 (2CH, Ph), 128.7 (2CH, Ph), 128.8 (CH, Ar), 140.3 (C, Ph), 142.6 (C, Ph), 143.9 (C), 158.7 (C). IR (neat): 3401, 3062, 2923, 2854, 2360, 1527, 1481, 1257 cm^{-1}. ESI-MS: Calcd for $C_{33}H_{43}N_2OS$ $(M + H)^+$ 515.3096, found 515.3107. **12'a** (Table 1, run 12)**:** Colorless oil; ^{1}H NMR ($CDCl_3$, 600.1 MHz): δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.25-1.30 (m, 16H), 1.35-1.39 (m, 2H), 1.62-1.67 (m, 2H), 2.72 (brs, 1H, OH), 2.94 (ddd, *J* = 6.8, 8.2, 12.9 Hz, 1H), 3.24 (ddd, *J* = 6.3, 8.2, 13.0 Hz, 1H), 4.62 (d, *J* = 8.4 Hz, 1H, H-4), 4.69 (d, *J* = 8.4 Hz, 1H, CH-O), 6.12 (d, *J* = 7.4 Hz, 1H), 6.75 (ddd, *J* = 2.0, 6.5, 7.4 Hz, 1H, Ar), 7.02 (d, *J* = 7.0 Hz, 2H, Ph), 7.17-7.23 (m, 6H, Ar), 7.31 (dd, *J* = 7.5, 8.0 Hz, 2H, Ph), 7.46 (d, *J* = 7.8 Hz, 2H, Ph). ^{13}C NMR ($CDCl_3$, 150.9 MHz): δ 14.1 (CH_3), 22.7 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.3 (CH_2), 31.9 (CH_2), 69.8 (CH, C-4), 74.3 (CH, C-O), 122.0 (C), 123.2 (CH, Ar), 123.8 (CH, Ar), 126.7 (CH, Ar), 127.0 (2CH, Ph), 127.1 (CH, Ar), 127.4 (2CH, Ph), 127.9 (CH, Ar), 128.2 (2CH, Ph), 128.7 (2CH, Ph), 128.8 (CH, Ar), 140.0 (C, Ph),

142.4 (C, Ph), 144.8 (C), 157.3 (C). IR (neat): 3216, 3062, 2923, 2854, 2360, 1527, 1481, 1257 cm^{-1}. ESI-MS: Calcd for $C_{33}H_{42}N_2NaOS$ $(M + Na)^+$ 537.2916, found 537.2909.

9. The structures **16**-**19** were determined spectroscopically (in particular, the observed correlation for NOESY and HMBC measurements between H-4/HC(Ar-N(3)) and H-4/C-N(3), respectively).
10. Similar observations and arguments have been reported. See lit.[1f] and G. Blanco, N. Segui, J. M. Quintela, C. Peinador, M. Chas, and R. Toba, *Tetrahedron*, 2006, **62**, 11124.