HETEROCYCLES, Vol. 82, No. 1, 2010, pp. 305 - 311. © The Japan Institute of Heterocyclic Chemistry
Received, 23rd June, 2010, Accepted, 26th July, 2010, Published online, 27th July, 2010
DOI: 10.3987/COM-10-S(E)66

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†

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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.

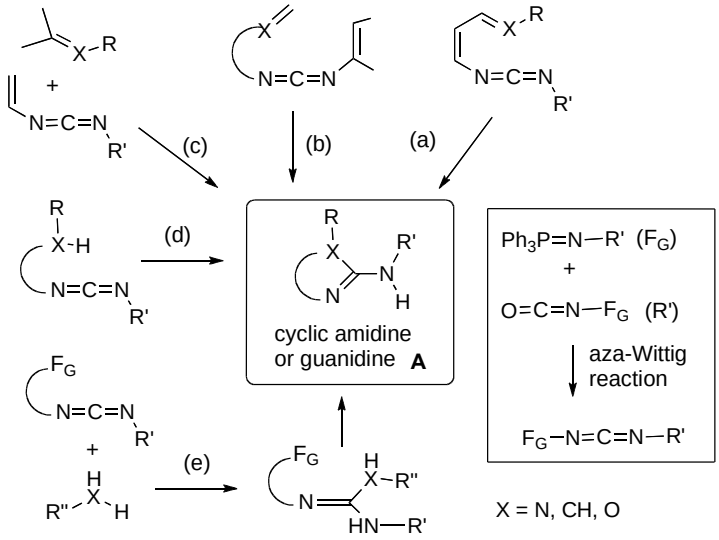
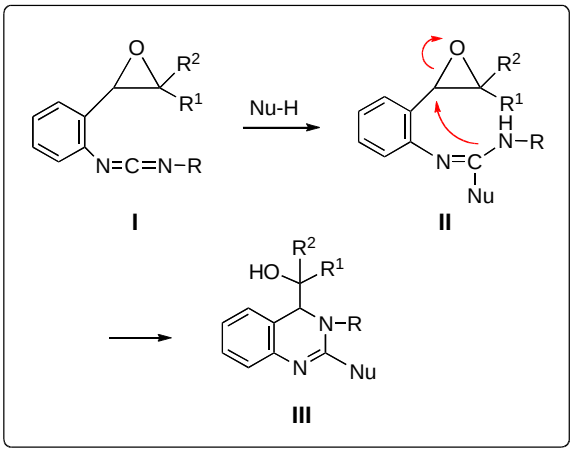


Chart 1. Various tandem cyclization pathways leading to cyclic amidines or guanidines

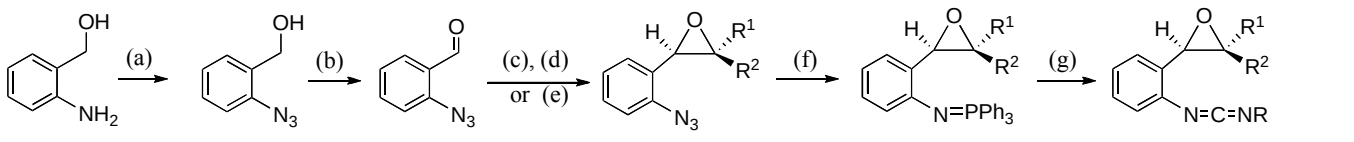


Scheme 1. Tandem nucleophilic addition /epoxy ring-opening cyclization

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*): $R^1 = H$, $R^2 = Ph$

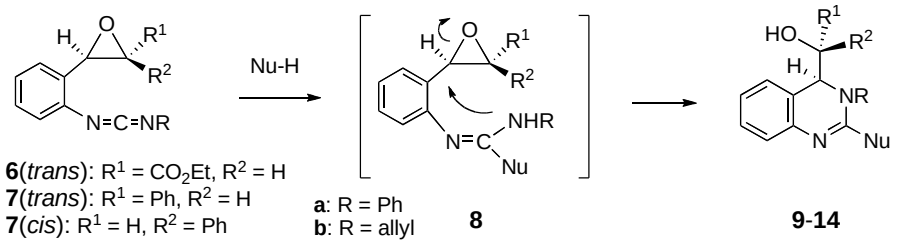
(a) i) $NaNO_2$/aq.HCl, 1 h; ii) NaN_3, 1 h/aq.HCl, 0 °C, 64%
(b) PCC, rt, 2 h/CH_2Cl_2, 94% (c) $ClCH_2CO_2Et$, Na/EtOH, rt, 4 h, 99%
(d) BnBr, tetrahydrothiophene, K_2CO_3/MeCN, rt, 3 d, 80% (e) i) $PhCH=PPh_3$, ii) *m*CPBA
(f) Ph_3P/CH_2Cl_2, 96% (g) R-NCO/CH_2Cl_2, 0 °C-rt, 1-4 h, 88-99%

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

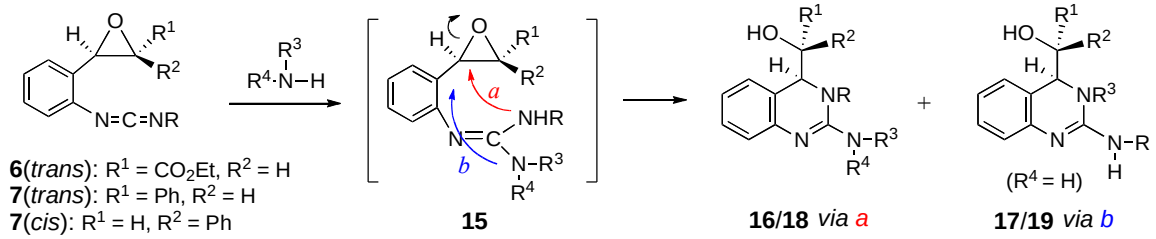
Run	Carbo-diimide	R^1	R^2	R	Nu-H	Base (equiv)	Reaction Conditions	Product[a] (Yield/%)
1	**6a**	CO_2Et	H	Ph	MeOH	MeONa (0.1)	rt, 3 d, CH_2Cl_2	**9a** (61)
2	**6b**	CO_2Et	H	allyl	MeOH	MeONa (0.2)	rt, 48 h, CH_2Cl_2	**9b** (37)
3	**6a**	CO_2Et	H	Ph	*o*-ClPhOH	Na (1.0)	rt, 2 h, CH_2Cl_2	**9c** (54)
4	**7a**	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) δ14.1 (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): δ0.87 (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): δ14.1 (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.