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Ring-Closing Olefin Metathesis for the Synthesis of 1,8-Diazabicyclo[4.3.0]non-3-ene-7,9-diones

Alexey B. Dyatkin*

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, P.O.Box 368, Ridgefield, CT 06877 USA

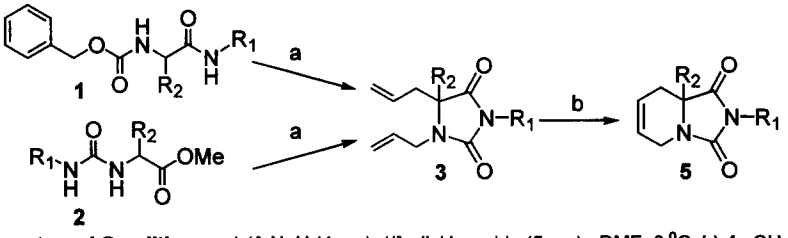
Abstract. A novel method for the efficient synthesis of 1,8-diazabicyclo[4.3.0]non-3-ene-7,9-diones **5** (bicyclic hydantoins) starting from ureas or Z-protected aminoacids has been developed. The key step is a ring-closing metathesis (RCM) reaction of diallyl substituted hydantoins **3** catalyzed by the ruthenium-carbene complex bis(tricyclohexylphosphine)benzilidine ruthenium dichloride (**4**). © 1997 Elsevier Science Ltd.

Grubbs[1] and Schrock[2] have reported the use of efficient catalysts for the metathesis of nonconjugated olefins to form cyclic compounds. The ring-closing metathesis (RCM) reaction has thus become a powerful tool for organic synthesis. This was effectively demonstrated in the synthesis of a variety of carbocycles[3] and heterocycles[4] and in the total synthesis of natural products.[5]

We report herein the application of the commercially available[6] ruthenium carbene complex bis (tricyclohexylphosphine)benzilidine ruthenium dichloride (**4**) for the synthesis of 1,8-diazabicyclo[4.3.0]non-3-ene-7,9-diones **5**. These compounds have attracted the attention of a number of research groups due to their potential biological application and as templates in organic synthesis; for the preparation of these compounds two major approaches are known.[7, 8]

We developed an alternative route to produce 1,8-diazabicyclo[4.3.0]non-3-ene-7,9-diones in moderate to good yields. Starting compounds for this synthesis can be easily prepared by the tandem cyclization-allylation reaction of Z-protected aminoacids **1**[9] or ureas **2**[10] **(Scheme 1)**.

Scheme 1.



Reagents and Conditions: a) (*i*) NaH (4 eq.) (*ii*) allyl bromide (5 eq.), DMF, 0 °C. b) **4**, CH_2Cl_2, reflux

The addition of substrate **1** or **2** to a suspension of NaH (4 eq.) in dry DMF at 0°C followed by allyl bromide (5 eq.) provided the formation of 1,5-diallylhydantoins **3** in 70-85% yield. Derivatives of glycine (R^2= H in **1** and **2**) give 1,5,5-triallylated products **3d** (R^2 = allyl).

Intramolecular RCM reactions were performed in refluxing methylene chloride with 10 mol % of **4** as a catalyst,[11] and in all cases conversion of **3** was more than 95%. Results are presented in the **Table 1**.[12] Surprisingly, compound **3d** did not form any spirocyclic product, the lower yield in this case probably can be explained by cross-coupling polymerization.

In summary, we have described a short and convenient method for the synthesis of 1,8-diazabicyclo [4.3.0]non-3-ene-7,9-diones **5** (bicyclic hydantoins) starting from simple commercially available materials.

Table 1. Synthesis of 1,8-Diazabicyclo[4.3.0]non-3-ene-7,9-diones **5** by RCM reaction of **3** catalyzed by Bis(tricyclohexylphosphine)benzilidine ruthenium dichloride **4**

Entry, **5**	R^1	R^2	Yield, %
a	Phenyl	Benzyl	52
b	4-$MeOC_6H_4CH_2$	iso-Propyl	63
c	t-Butyl	iso-Butyl	55
d	4-$MeOC_6H_4CH_2$	Allyl	45
e	4-$MeOC_6H_4CH_2$	Benzyl	74
f	cyclo-Hexyl	Methyl	65
g	Phenyl	N-Allyl-3-indolylmethyl	65

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* Present address: R. W. Johnson Pharmaceutical Research Institute, Drug Discovery, Spring House, PA 19477, USA

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11. In the typical procedure for the synthesis of **5** a solution of **3** (1 mmol) in 20 ml of dry CH_2Cl_2 under Ar atmosphere was heated to reflux and a solution of **4** (0.01 mmol) in 5 ml CH_2Cl_2 was added by syringe in one portion. The reaction mixture was refluxed overnight, evaporated and the remaining brown residue was subjected to column chromatography (silica, hexanes-ethyl acetate mixture as eluent).
12. The new compounds **3** and **5** were characterized by NMR and PB-EI MS spectra and gave elemental analyses in accord with the calculated values.
    Selected data for **5g**: white crystals, m.p. 130-132°C, ^1H NMR (270 MHz, $CDCl_3$) δ 7.60 (d, J=7.8Hz, 1H), 7.28-7.18 (m, 6H), 6.89 (s, 1H), 6.83-6.79 (m, 2H), 5.95-5.84 (m, 3H), 5.10 (dd, J= 10.3 and 1.2Hz, 1H), 4.93 (dd, J= 17.0 and 1.2Hz, 1H), 4.65 (dt, J= 5.3 and 1.5Hz, 2H), 4.53-4.40 (m, 1H), 3.92-3.81 (m, 1H), 3.47 (d, J= 14.9Hz, 1H), 3.32 (d, J= 14.8Hz, 1H). ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 175.3, 153.6, 135.9, 133.0, 131.3, 128.6, 128.0, 127.8, 126.8, 126.0, 122.8, 122.3, 121.8, 119.3, 118.8, 117.1, 109.5, 107.5, 61.5, 48.5, 38.1, 31.1, 29.7. PB-EI MS: m/z 397 (M^+). Anal. Calcd. for $C_{25}H_{23}N_3O_2$: C, 75.55; H, 5.83; N, 10.57. Found: C, 75.29; H, 5.89; N, 10.49.

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