ORGANIC LETTERS

2002
Vol. 4, No. 5
839−841

# Domino Reactions of Amidines with Methyl 2-Chloro-2-cyclopropylideneacetate as an Efficient Access to Cyclobutene-Annelated Pyrimidinones†

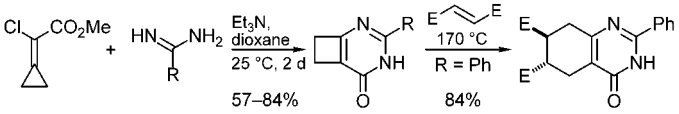
**Marcus W. Nötzel, Karsten Rauch, Thomas Labahn, and Armin de Meijere***

*Institut für Organische Chemie der Georg-August Universität Göttingen, Tammannstrasse 2, D-37077 Göttingen, Germany*

*armin.demeijere@chemie.uni-goettingen.de*

**Received January 10, 2002**

## ABSTRACT

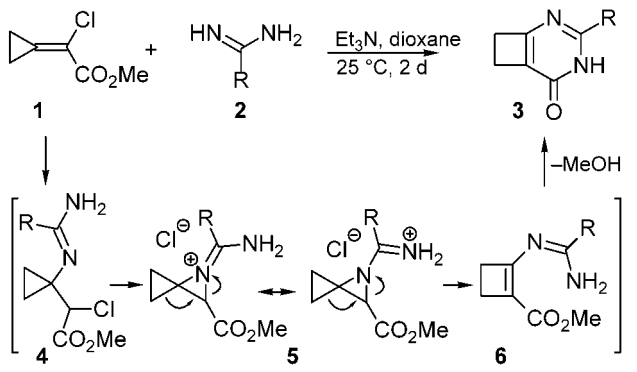



**An efficient one-step synthesis of 2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-ones 3 from methyl 2-chloro-2-cyclopropylideneacetate (1) and amidines 2a–c as well as *N*,*N*-dimethylguanidine (2d) is described. Similar to the benzocyclobutenes, the cyclobutene-annelated pyrimidones 3 undergo thermal ring opening and the resulting *o*-quinodimethane analogues readily cycloadd dienophiles to yield tetrahydroquinazolone derivatives.**

Recently we reported a versatile method for the synthesis of spirocyclopropane-annelated thiazoline-4-carboxylates and thiazinones proceeding via a Michael addition of thioamides onto the reactive Michael acceptor methyl 2-chloro-2-cyclopropylideneacetate (**1**) with subsequent ring closure by intramolecular nucleophilic substitution.[1] It was conceivable that amidines would react by the same mode to yield spirocyclopropane-annelated imidazoline-4-carboxylates and dihydropyrimidones, i.e., potential precursors to compounds with biological activities.[2,3] Therefore it was of interest to study the addition of amidines to **1**.

When a mixture of methyl 2-chloro-2-cyclopropylidene-acetate (**1**) and formamidine (**2a**) in dioxane in the presence of 4 equiv of triethylamine was stirred for 2 days at ambient temperature, instead of the expected imidazoline derivative, the 2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**3a**) was isolated in 57% yield (Scheme 1). The structure could be assigned on the basis of its $^{1}$H and $^{13}$C NMR as well as MS data, and it was rigorously proved by an X-ray crystal structure analysis (Figure 1).[4]

**Scheme 1**

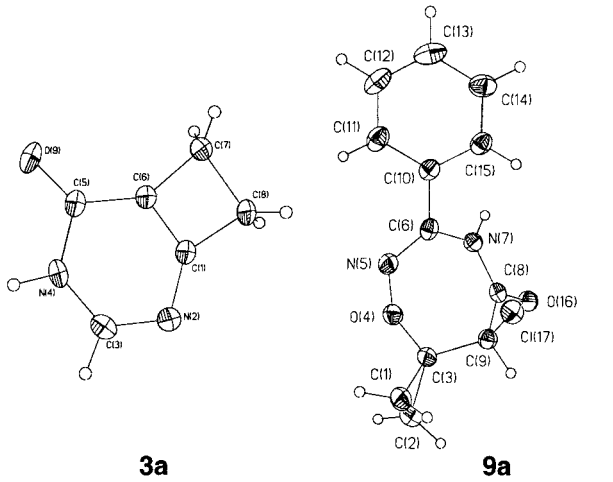



† Part 75 in the series *Cyclopropyl Building Blocks for Organic Synthesis*. For part 74, see: Emme, I.; Redlich, S.; Labahn, T.; Magull, J.; de Meijere, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 786.

(1) Nötzel, M. W.; Labahn, T.; Es−Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2001**, 3025.

(2) A number of imidazolinone derivatives are known to be antagonists of angiotensin II. Bernhart, C. A.; Perreaut, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J.-L. A.; Clément, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E.; Vignal, M.-A.; Gougat, J.; Guiraudou, P. R.; Lacour, C. A.; Roccon, A.; Cazaubon, C. F.; Brelière, J.-C.; Le Fur, G.; Nisato, D. *J. Med. Chem.* **1993**, *36*, 3371.

10.1021/ol025530+ CCC: $22.00 
**Published on Web 02/07/2002**




**3a** **9a**

**Figure 1.** Structures of 2,4-diazabicyclo[4.2.0]octa-1(6),2-dien-5-one (**3a**) and 9-chloro-6-phenyl-5,7-diaza-4-oxaspiro[2.6]non-5-en-8-one (**9a**) in the crystals.

Benzamidine (**2b**), *p*-methylbenzamidine (**2c**), and *N*,*N*-dimethylguanidine (**2d**) under the same conditions gave the corresponding pyrimidinones **3b**−**d** in yields ranging from 57 to 84%, whereas the reaction with unsubstituted guanidine (**2e**) led only to decomposition (Table 1).

**Table 1.** Preparation of Cyclobutene-Annelated Pyrimidinones **3** from Amidines **2** and Methyl 2-Chloro-2-cyclopropylideneacetate (**1**)

| entry | amidine | R | product | yield (%) |
|---|---|---|---|---|
| 1 | **2a** | H | **3a** | 57 |
| 2 | **2b** | Ph | **3b** | 84 |
| 3 | **2c** | *p*-Me-Ph | **3c** | 79 |
| 4 | **2d** | $NMe_2$ | **3d** | 59 |
| 5 | **2e** | $NH_2$ | **3e** | *a* |

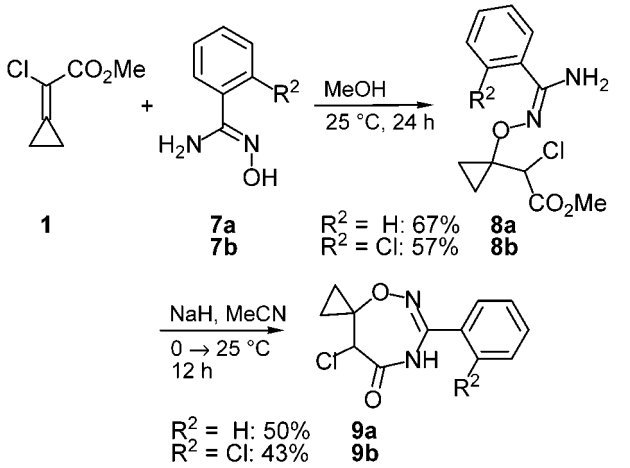
[a] Decomposition.

Obviously the primary Michael adducts **4**, resulting from the addition of amidines **2** onto **1**, under the employed conditions more rapidly rearrange to cyclobutenecarboxylates **6** than cyclize to yield a five-membered heterocycle by intramolecular nucleophilic substitution, as the primary adducts of **1** and carboxamides[5] and thiocarboxamides do under basic conditions.[1] The cyclobutenecarboxylates **6** then undergo, by an intramolecular attack of the amino group on the methyl ester moiety, cyclization leading to the pyrimidinones **3**. This type of rearrangement encountered for **4** has previously been observed for adducts of benzophenoneimine[6] and secondary as well as primary amines.[7] It is rationalized as occurring by way of neighboring group participation to form the stabilized aziridinium ion **5** which rearranges via cyclopropylcarbinyl to cyclobutyl cation ring enlargement (Scheme 1).[8]

Since oxygen substituents are less effective neighboring group participants than nitrogen-centered groups, the addition of *N*-hydroxyamidines **7** instead of amidines **2** to **1** was expected to proceed without rearrangement, because they would add with the more nucleophilic hydroxy group attacking on **1**.[9]

Indeed, when a mixture of methyl 2-chloro-2-cyclopropylideneacetate (**1**) and *N*-hydroxybenzamidine (**7a**) in methanol was stirred for 24 h at ambient temperature, the Michael adduct methyl 2-chloro-2-(phenylcarboximidoylaminooxycyclopropyl)acetate (**8a**) was isolated in 67% yield. When **8a** was deprotonated with sodium hydride in acetonitrile at 0 °C, 9-chloro-6-phenyl-5,7-diaza-4-oxaspiro[2.6]non-5-en-8-one (**9a**) was formed by attack of the amide on the methyl ester moiety (Scheme 2). Neither intramolecular nucleophilic

**Scheme 2**




substitution of the chlorine atom nor rearrangement was observed. The structure was assigned on the basis of its $^1H$ and $^{13}C$ NMR as well as MS data, and it was rigorously proved by an X-ray crystal structure analysis of **9a** (Figure

(3) A compound with a spirocyclopropane-annelated imidazoline moiety inhibits the specific binding of angiotensin II at a concentration of less than 50 nM. Cremer, G.; Muller, J. C. (Synthelabo S. A., Fr). U.S. (1995), 7 pp. Cont.-in-part in U.S. Ser. No. 2,502, abandoned. CODEN: USXXAM US 5457112 A 19951010. Application: US 93-165648 19931213. Priority: FR 92-15038 19921214; US 93-2502 19930106. CAN 124:117321 AN 1995:913758.

(4) Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-163584 (**3a**) and CCDC-163585 (**9a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. (a) Sheldrick, G. M. *Acta Crystallogr., Sect A* **1990**, *46*, 467. (b) Sheldrick, G. M. SHELXL-93; Program for Crystal Structure Refinement, University of Göttingen, 1993.

(5) Nötzel, M. W.; Tamm, M.; Labahn, T.; Noltemeyer, M.; Es−Sayed, M.; de Meijere, A. *J. Org. Chem.* **2000**, *65*, 3850.

(6) Wessjohann, L.; Giller, K.; Zuck, B.; Skattebøl, L.; de Meijere, A. *J. Org. Chem.* **1993**, *58*, 6442.

(7) Tamm, M.; Thutewohl, M.; Ricker, C. B.; Bes, M. T.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, 2017.

(8) (a) Mazur, R. H.; White, W. N.; Semenov, D. A.; Lee, C. C.; Silver, M. S.; Roberts, J. D. *J. Am. Chem. Soc.* **1959**, *81*, 4390. (b) Olah, G. A.; Jeuell, C. L.; Kelly, D. P.; Porter, R. D. *J. Am. Chem. Soc.* **1972**, *94*, 146.

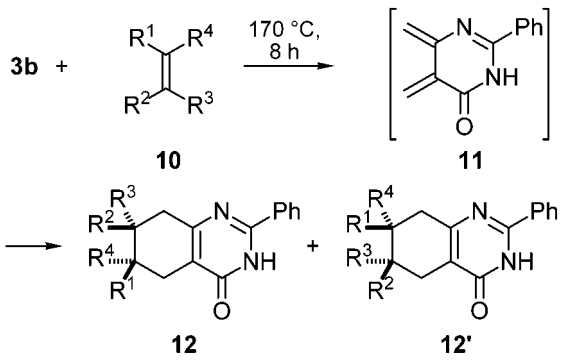
(9) Lwowski, W. *Angew. Chem.* **1958**, *70*, 483.

1).[4] Under the same conditions, *N*-hydroxy-*o*-chlorobenzamidine (**7b**) gave **8b** (57%) which could be cyclized to **9b** in 43% yield.

The cyclobutene-annelated pyrimidinones **3** resemble heteroanalogues of benzocyclobutenes, and as such they should be able to undergo ring opening to heteroanalogues of *o*-quinodimethanes which ought to be trapped by dienophiles.[10] Indeed, when the derivative **3b** was heated at 170 °C with dimethyl fumarate **10c** for 8 h, the [4 + 2] cycloadduct **12c** of the in situ formed 5,6-dimethylenetetrahydropyrimidinone **11** was isolated in 84% yield.

A whole series of dienophiles, **10a**−**e**, reacted with **3b** under the same conditions to give the Diels−Alder adducts of **11** in 47−84% yield (Scheme 3).[11] Dimethyl maleate

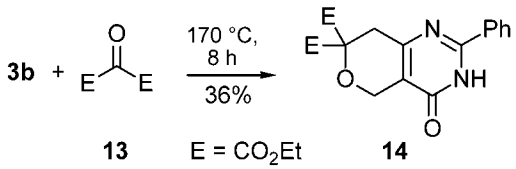
**Scheme 3**




| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | **12/12'** (%) | ratio |
|---|---|---|---|---|---|---|
| **a** | $CO_2Me$ | H | H | H | 78 | 2.4:1 |
| **b** | CN | H | H | H | 47 | 2:1 |
| **c** | $CO_2Me$ | H | $CO_2Me$ | H | 84 | — |
| **d** | $CO_2Me$ | $CO_2Me$ | H | H | 73[a] | — |
| **e** | $CO_2Me$ | H | Ph | H | 82[b] | 2:1 |

[a] Mixture of *cis*- (**12d**) and *trans*-dicarboxylate **12c** in the ratio of 4.8:1. [b] Pure *trans*-isomer.

furnished a 4.8:1 mixture of the *cis*- (**12d**) and *trans*-isomer **12c**. The unsymmetrically substituted dienophiles methyl acrylate (**10a**), acrylonitrile (**10b**), and methyl cinnamate (**10e**) all led to inseparable mixtures of two regioisomeric cycloadducts **12** and **12′**. For **12e**/**12′e** the major isomer was assigned to be **12e** by an HMBC (heteronuclear multi bond correlation) 2D-NMR measurement, and for the other products **12a**/**12′a** and **12b**/**12′b** the major isomers were assumed to be of the same type, i.e., **12a** and **12b**, respectively. Diethyl mesoxalate (**13**) also reacted with **3b** at 170 °C to furnish a single adduct, **14**, albeit in moderate yield (36%). The structure of **14** (Scheme 3) was established on the basis of its HMBC-2D-NMR spectrum.




Thus, methyl 2-chloro-2-cyclopropylideneacetate (**1**) upon treatment with amidines **2** under basic conditions undergoes a domino transformation involving a Michael addition followed by a ring-enlarging rearrangement and cyclization to afford cyclobutene-annelated pyrimidinones **3**. On the other hand, *N*-hydroxyamidines **7** add onto **1** to give 2-chloro-2-cyclopropylacetate derivatives **8** which, after deprotonation cyclize to seven-membered heterocycles **9**. The [4 + 2] cycloadditions of dienophiles **10** and **13** to 5,6-dimethylenetetrahydropyrimidinones of type **11** in situ generated from the new cyclobutene-annelated pyrimidinones **3** provide easy access to tetrahydroquinazolone derivatives and heteroanalogues of types **12** and **14**, respectively. This new route to potentially biologically active heterocycles of types **12** and **14**, which are essentially adenosine analogues, is shorter and provides significantly better overall yields (e.g., 66 vs 29% for **12a**, 71 vs 31% for **12c**) than a previously published one.[11] This chemical utility of compounds **3** also significantly exceeds that of cyclobutane-annelated fluorouracils (fluoropyrimidindiones) which are accessible by photochemical [2 + 2] cycloaddition of certain alkenes to fluorouracil.[12]

**Acknowledgment.** This work was supported by the Bayer AG and the Fonds der Chemischen Industrie as well as through generous gifts of chemicals by the BASF AG. The authors are indebted to Dr. André Savtchenko, Göttingen, for his help in assigning the regioisomers of **12e**/**12′e** and to Dr. Burkhard Knieriem, Göttingen, for his careful reading of the final manuscript.

**Supporting Information Available:** Experimental procedures as well as physical and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL025530+

(10) The in situ [4 + 2] cycloaddition of *o*-quinodimethanes from benzocyclobutenes is a well-established synthetic method. For a review, see: Michellys, P. Y.; Pellisier, H.; Santelli, M. *Org. Prep. Proced. Int.* **1996**, *28*, 545.

(11) 5,6-Dimethylenedihydropyrimidin-4-ones of type **11** have previously been generated by thermal $SO_2$ extrusion from corresponding substituted pyrimidone-fused 3-sulfolenes which are accessible in two steps from methyl 4-oxotetrahydrothiophene-3-carboxylate. Cf. Tomé, A. C.; Cavaleiro, J. A. S.; Storr, R. C. *Tetrahedron* **1996**, *52*, 1723.

(12) Swenton, J. S.; Jurcak, J. G. *J. Org. Chem.* **1988**, *53*, 1530.