Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Intramolecular cycloaddition of *N*-phthalimidoaziridines to double and triple carbon–carbon bonds

Alena S. Pankova, Vladimir V. Voronin, Mikhail A. Kuznetsov *

Department of Chemistry, Saint-Petersburg State University, Universitetskiy pr. 26, Saint-Petersburg 198504, Russian Federation

A B S T R A C T

Thermolysis of 3-(2-allyloxyphenyl)- or 3-(2-propargyloxyphenyl)-1-phthalimidoaziridine-2-carboxylic acid derivatives results in stereospecific intramolecular cycloaddition of intermediate *N*-phthalimidoazomethine ylides to double or triple carbon–carbon bonds. This leads to condensed *N*-phthalimidopyrrolidines, *N*-phthalimidopyrrolines, or products of their subsequent transformations. On the other hand, thermolysis of similar dimethyl 3-aryl-1-phthalimidoaziridine-2,2-dicarboxylates gives exclusively 5-methoxyoxazoles, the products of a competitive 1,5-dipolar electrocyclization.

© 2009 Elsevier Ltd. All rights reserved.

1,3-Dipolar cycloaddition of azomethine ylides is a general method for the synthesis of five-membered nitrogen heterocycles.[1–3] The intramolecular version of this reaction leads to bi- and polycyclic structures, thereby increasing the synthetic applicability of this transformation. The addition of aziridines to active dipolarophiles resulting in five-membered nitrogen-containing heterocycles was reported in 1965.[4] The process starts with thermally or photochemically induced cleavage of an aziridine carbon–carbon bond to give an azomethine ylide, followed by its concerted addition to a dipolarophile.[1–3] The use of *N*-aminoaziridine derivatives could open a direct route to various *N*-aminoheterocycles; however, examples were described mostly with tri- and tetra-substituted *N*-phthalimidoaziridines.[5–8] We have shown that the intermolecular cycloaddition of some disubstituted *N*-phthalimidoaziridines proceeds in a stereospecific and diastereoselective manner under thermolysis conditions in good yields.[9,10] Taking our findings into account, we decided to investigate the possibility of a similar intramolecular thermal reaction. Herein we report hitherto unknown examples of a thermal intramolecular cycloaddition of *N*-phthalimidoaziridines possessing a side-chain C–C double or triple bond. Some of the obtained compounds contain the hexahydrochromeno[4,3-*b*]pyrrole scaffold as found in various natural compounds.[11,12]

The *N*-phthalimidoaziridines **6–9a,b** bearing unsaturated side chains were synthesized from salicylic aldehyde via *ortho*-(allyloxy)- and *ortho*-(propargyloxy)cinnamic acids and benzylidenemalonic acid derivatives **1–4a,b**[13] using a standard oxidative
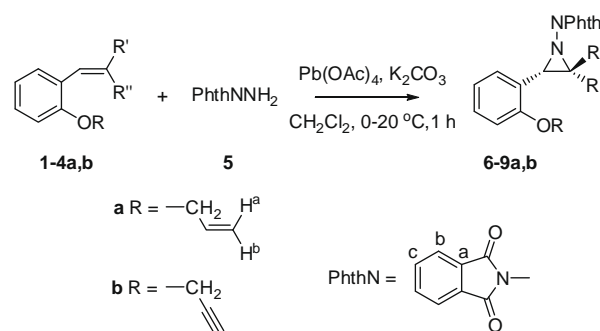
Scheme 1. Oxidative addition of *N*-aminophthalimide to unsaturated compounds **1–4a,b**.

Table 1
Oxidative addition of *N*-aminophthalimide to unsaturated compounds **1–4a,b** via Scheme 1

Entry	Starting compound	R′	R″	Product	Yield[a] (%)
1	**1a**	CO_2Me	H	**6a**	68
2	**1b**	CO_2Me	H	**6b**	70
3	**2a**	CN	H	**7a**	39
4	**2b**	CN	H	**7b**	48
5	**3a**	$CONEt_2$	H	**8a**	41
6	**3b**	$CONEt_2$	H	**8b**	77
7	**4a**	CO_2Me	CO_2Me	**9a**	35
8	**4b**	CO_2Me	CO_2Me	**9b**	74

[a] Yield of isolated products.

* Corresponding author. Tel.: +7 812 428 6779; fax: +7 812 428 6939.
E-mail address: mak@mail.wplus.net (M.A. Kuznetsov).
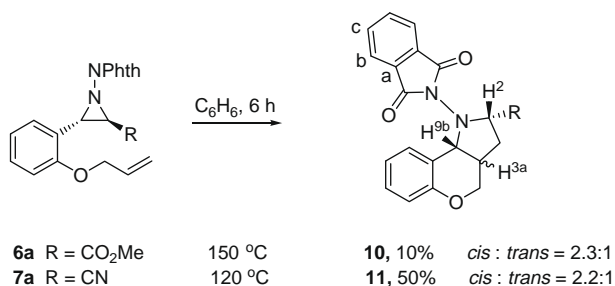
Scheme 2. Thermolysis of aziridines **6a** and **7a**.

aminoaziridination procedure[14] (Scheme 1 and Table 1). This reaction affects only the styrene C=C bond of these compounds and is in full agreement with the well-known low activity of the triple and non-conjugated terminal double bonds in such transformations.[15]

Electron-withdrawing substituents on the aziridine ring should promote ring-opening to a 1,3-dipole with a partial negative charge on the carbon atoms. Therefore, we chose CN, CO_2Me, and $CONEt_2$ groups along with a phenyl group that efficiently delocalizes both negative and positive charges. The length of the unsaturated side chain ensures the formation of an unstrained condensed system of five- and six-membered rings. The spatial proximity of the interacting fragments allows us to use non-activated C=C and C≡C bonds[16] giving access to both saturated and unsaturated heterocycles and also allows a study of the stereochemical aspects of the cycloaddition process.

An important property of most N-aminoaziridine derivatives is the high barrier to endocyclic nitrogen atom inversion, which usually leads to the co-existence of two invertomers on the NMR time scale.[17] According to ^{1}H NMR spectra at room temperature, aziridines **6–8a,b** exist as a mixture of two invertomers with a strong prevalence for one of them (the ratio is ~95:5). The signals of the aziridine protons of the main invertomer are located at higher fields than those of the minor one. Reliable identification of the signals in the ^{13}C NMR spectra can only be achieved for the main invertomer. Aziridines **9a,b** exist as single invertomers. According to the small vicinal coupling constants in the aziridine rings (^3J = 5.0–5.1 Hz for the main invertomer and 5.6–6.0 Hz for the minor one), the trans-orientation of the substituents in the starting olefins **1–3a,b** is retained in the aziridines **6–8a,b**.

The non-equivalence of the ethyl groups of the diethylamide fragment in aziridines **8a,b** became apparent in their NMR spectra due to hindered rotation about the amide C–N bond.

Thermolysis of compounds **6–9a,b** was carried out in benzene. The optimal reaction temperature was determined for each substrate by gradual heating starting from ambient temperature and by monitoring the reaction by TLC.

Compounds **6a** and **7a** gave the expected corresponding condensed N-phthalimidopyrrolidine derivatives **10** and **11** as mixtures of two diastereoisomers in the ratio ~2:1 (Scheme 2). The most important distinction between these products is the value of the vicinal coupling constant ^3J (H–**3a**–H–**9b**) in their ^{1}H NMR spectra, which is 5.1 Hz for the major component and 11.1 Hz for the minor one in the mixture of compounds **10**, and 5.8 Hz and 10.2 Hz in the mixture of **11**, respectively. A comparison of these values with the literature data[12] for similar structures allowed us to conclude that the major components of these mixtures are cis-orientated at the five- and six-membered ring junctions, whereas the minor diastereomers are trans-fused. Fractional crystallization of the mixture of products **10** from ethanol afforded pure cis-isomer **10**. To our disappointment, this method failed in the case of the mixture of **11**. The low yield of tricyclic esters **10** seems to be a consequence of the competition between 1,3-dipolar cycloaddition and other secondary processes, for example, rearrangements.[5–8,18]

The characteristic features of the ^{13}C NMR spectra of compounds **10** and **11**, as well as of the other sterically hindered N-phthalimidopyrrolidine and N-phthalimidopyrroline derivatives obtained,[9,10] are the absence of C(O)N carbon signals and broadening of the C-a signals of the phthalimide moiety. This is due to slow rotation of this group around the N–N bond resulting in non-equivalent halves of the phthalimide fragment.

The orientation of the R substituents on C-2 in compounds **10** and **11** was proved from the 2D NOESY spectra, which allowed confirmation of the signal assignment in the ^{1}H NMR spectra as well. Such positioning of the substituents is in accordance with a thermally allowed conrotatory ring-opening of the trans-aziridine into the (E,E)- or (Z,Z)-azomethine ylide followed by a concerted cycloaddition reaction. Two different plausible cycloaddition transition states give rise to the formation of diastereoisomers with either cis or trans ring junctions at the five- and six-membered rings (Scheme 3).

A surprising result was obtained on thermolysis of aziridine **8a**. In this case, we observed no traces of the expected cycloadduct in the ^{1}H NMR spectrum of the reaction mixture after heating. The only isolated product (apart from phthalimide and 2-(allyloxy)benzaldehyde) was chromenopyridine **12** (Scheme 4).

The structure and composition of compound **12** were proved from its mass spectrum (molecular ion peak with m/z 254), ^{1}H and ^{13}C NMR data, the 2D NOESY spectrum, and elemental analysis. In the ^{1}H NMR spectrum the signals of the o-C_6H_4 moiety (δ = 6.92–8.06 ppm), two ethyl groups, the OCH_2 group as well as two doublets due to the pyridine ring protons (^4J = 2.9 Hz) were easily identified. The position of the NEt_2 substituent was in agree-
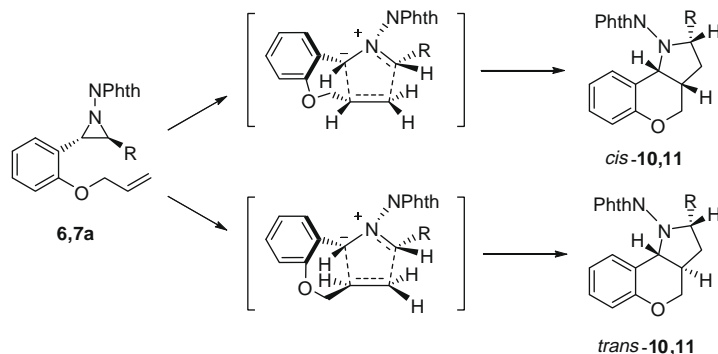
Scheme 3. Transition states en route to cis- and trans-**10**, **11**.
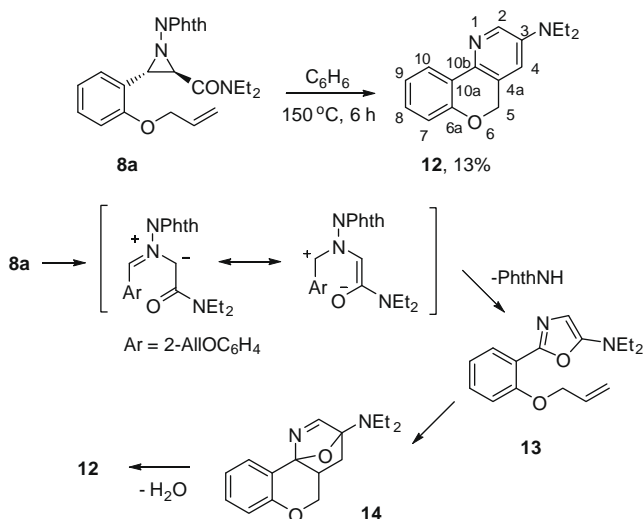
Scheme 4. Thermolysis of aziridine **8a** and a plausible mechanism for the formation of chromenopyridine **12**.

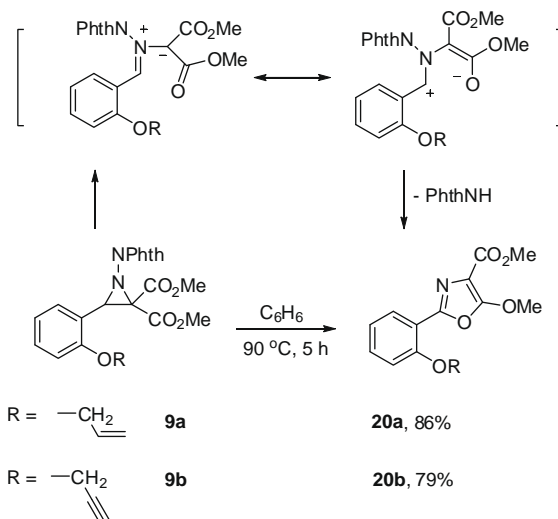**Scheme 6.** Thermolysis of aziridines **9a,b**.

ment with the observed NOE between the NCH$_2$ protons and both pyridine ring protons (H-2 and H-4).

A possible mechanism for the formation of compound **12** is depicted in Scheme 4. First, transformation of aziridine **8a** to oxazole **13** occurs[18] followed by intramolecular Diels–Alder addition accompanied by elimination of a water molecule from the intermediate **14**.

Thermolysis of aziridines **6–8b** with a triple bond in the side chain led to the expected products of the 1,3-dipolar cycloaddition in all cases. Moreover, aziridines **6b** and **8b** gave mixtures of pyrrolines **15** and **18** and pyrroles **16** and **19**, but aziridine **7b** gave pyrroline **17** only (Scheme 5). The formation of pyrroles **16** and **19** seems to be a result of the loss of phthalimide from pyrrolines **15** and **18** under thermolysis conditions.

The assignment of the H-2, H-3, and H-9b signals located in the region δ = 5.3–5.9 in the ^{1}H NMR spectra of pyrrolines **15**, **17**, and **18** was based on the values of $^1J_{C-H}$ (180 Hz for the highest field signal in this region, which we assigned to the sp^2-carbon atom C-3, and 147 Hz and 156 Hz for the two other signals), and COSY C–H and 2D NOESY data. In the 2D NOESY spectra of compounds **15**, **17**, and **18**, the least intense cross-peak corresponds to the H-3 and H-9b protons, which are distant from each other. Similar NOE intensities for the pair of neighboring protons H-2, H-3 and for the pair H-2, H-9b indicate a *cis*-arrangement of the latter protons and are in agreement with the generation of the *cis*-azomethine ylide from the *trans*-aziridine followed by a concerted cycloaddition process.

It is noteworthy that similarly substituted aziridines with double **6–8a** and triple **6–8b** bonds in the side chains require the same reaction times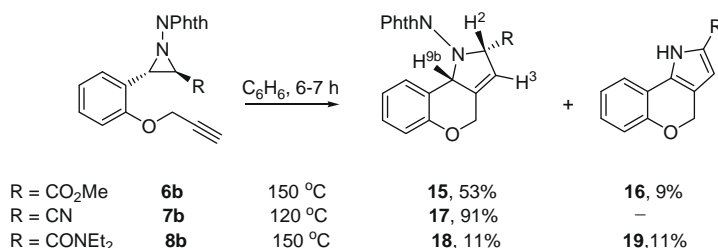, and the optimal reaction temperatures [120 °C for compounds with a CN group (**7a,b**) and 150 °C for compounds with CO$_2$Me (**6a,b**) and CONEt$_2$ (**8a,b**) groups] are equal too. Based on this observation, we assume that the rate-determining step for the whole process could be cleavage of the aziridine to the azomethine ylide. If so, a lower reaction temperature for aziridines **7a,b** compared to aziridines **6a,b** and **8a,b** shows facilitation of the aziridine ring cleavage by the strong electron-withdrawing cyano group, which improves the stability of the azomethine ylide. It is also in agreement with literature data.[6]

The difference in the yields of similarly substituted cycloaddition products for substrates with double and triple bonds can be explained taking into account steric factors. As has been shown above (Scheme 3), the plane of the double bond and the plane of the azomethine ylide fragment have to be near parallel in the transition state. At the same time, the triple bond needs no specific orientation due to its axial symmetry which increases the propensity for the azomethine ylide cycloaddition pathway compared to the competitive destruction processes.

Compounds **9a,b** with an additional electron-withdrawing substituent on the three-membered ring began to change noticeably at 80 °C, and at 90 °C the transformation was complete within 5 h. However, 5-methoxyoxazoles **20a,b** were isolated exclusively in both cases instead of the target intramolecular 1,3-dipolar cycloaddition products (Scheme 6). The unavoidable proximity of the generated azomethine ylide to the C=O bond of either of the ester groups, which leads to a rapid 1,5-dipolar electrocyclization, seems to have led to this result.

Thermally induced intramolecular cycloaddition of *N*-phthalimidoaziridines to double and triple carbon–carbon bonds is a general process for the described compounds leading to

Scheme 5. Thermolysis of aziridines **6–8b**.

R = CO$_2$Me	**6b**	150 °C	**15**, 53%	**16**, 9%
R = CN	**7b**	120 °C	**17**, 91%	–
R = CONEt$_2$	**8b**	150 °C	**18**, 11%	**19**, 11%

N-aminochromenopyrrolidine, *N*-aminochromenopyrroline, and chromenopyrrole derivatives, as a rule. The yields of the cycloadducts for substrates with C≡C bonds were usually higher than those of their C=C analogues. The configuration of the products is in agreement with a mechanism including thermally allowed conrotatory cleavage of the aziridine to the azomethine ylide followed by a concerted 1,3-dipolar cycloaddition. Competitive transformation of acylaziridines to oxazoles is possible due to the spatial proximity of a carbonyl group to the generated 1,3-dipole. Additional substituents on the aziridine ring along with increased electron-withdrawing character lead to milder reaction conditions.

Acknowledgments

Supplementary data

Representative experimental details for the synthesis and the characterization data for compounds **6–9a,b**, **10–12**, **15–19** and **20a,b** and 2D NOESY spectra of several compounds are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.015.

References and notes

1. Lown, J. W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons: New York, 1984; pp 653–732.
2. Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: Hoboken, 2003; pp 169–252.
3. Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809.
4. Heine, H. W.; Peavy, R. *Tetrahedron Lett.* **1965**, *35*, 3123–3126.
5. Foucaud, A.; Baudru, M. *C. R. Acad. Sci.* **1970**, *271 C*, 1613–1615.
6. Person, H.; Luanglath, K.; Baudru, M.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1976**, *11–12*, 1989–1992.
7. Charier, J.; Person, H.; Foucaud, A. *Tetrahedron Lett.* **1979**, *16*, 1381–1384.
8. Charrier, J.; Foucaud, A.; Person, H.; Loukakou, E. *J. Org. Chem.* **1983**, *48*, 481–486.
9. Kuznetsov, M. A.; Pankova, A. S.; Ushkov, A. V.; Selivanov, S. I. *Russ. J. Org. Chem.* **2008**, *44*, 1807–1815.
10. Pankova, A. S.; Ushkov, A. V.; Kuznetsov, M. A.; Selivanov, S. I. *Vestnik Sankt-Peterburgskogo Universiteta (Herold of Saint-Petersburg State University) Ser. 4* **2009**, *1*, 150–154.
11. Rossini, M.; Budriesi, R.; Bixel, M. G.; Bolognesi, M. L.; Chiarini, A.; Hucho, F.; Krogsgaard-Larsen, P.; Mellor, A.; Minarini, I. R.; Tumiatti, V.; Usherwood, P. N. R.; Melchiorre, C. *J. Med. Chem.* **1999**, *42*, 5212–5223.
12. Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175–7178.
13. The synthesis of compounds **1–4a,b** will be described elsewhere.
14. Gladstone, W. A. F.; Norman, R. O. C. *J. Chem. Soc. (C)* **1966**, 1536–1540.
15. Atkinson, R. S.; Kelly, B. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1627–1630.
16. DeShong, P.; Kell, D. A.; Silder, D. R. *J. Org. Chem.* **1985**, *50*, 2309–2315.
17. Atkinson, R. S.; Malpass, J. R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2242–2249.
18. Beletsky, E. V.; Kuznetsov, M. A. *Russ. J. Org. Chem.* **2009**, *45*, 1237–1248.