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Synthesis and thermal transformations of spiro-fused *N*-phthalimidoaziridines

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Dedicated to Professor Armin de Meijere on the occasion of his 75th birthday

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ABSTRACT

Oxidation of *N*-aminophthalimide in the presence of 2-arylideneinden-1,3-diones with electron-withdrawing substituents gives the corresponding 3-aryl-1-phthalimidospiro[aziridine-2,2′-indene]-1′,3′-diones in good yields. Heating these aziridines with standard dipolarophiles (*N*-phenylmaleimide, dimethyl acetylenedicarboxylate, maleate, and fumarate) leads, in most cases, to spiro[inden-2,2′-pyrrole] derivatives as products of 1,3-dipolar cycloaddition of the intermediate azomethine ylides with up to 70–95% yields in the case of *N*-phenylmaleimide. As is typical for 2-acylaziridines, the competing rearrangement into 2-aryl-4*H*-indeno[2,1-*d*][1,3]oxazol-4-ones prevails for less active dipolarophiles. Increasing the electron-releasing properties of the 3-aryl ring allows the observation of the push–pull effect of electron-donating and electron-withdrawing substituents on the ease of the three-membered ring-opening.

Functionalized aziridines serve as versatile building blocks for the synthesis of various nitrogen heterocycles via cleavage of the C–N or C–C bond.[1–3] *N*-Phthalimidoaziridines have the advantage of containing a masked *N*-amino group and their conversion into pyrrole and pyrrolidine derivatives was successfully demonstrated in our previous studies.[4–9] The underlying process for such transformations is the 1,3-dipolar cycloaddition of thermally generated azomethine ylides that can be realized in both inter- and intramolecular manners affording monocyclic or polycyclic condensed heterocycles, respectively. Obviously the involvement of spiro-fused aziridines in such a process can result in novel spiro-fused polycyclic heterocycles. Compounds of similar framework are of particular interest because they often form the central core of natural products and medicinal lead compounds. For example, the spiropyrrolidine moiety is found in numerous alkaloids[10–15] and antimycobacterial compounds as well as others featuring pharmacological properties.[16–18]

We therefore investigated a hitherto unknown approach to spiroheterocycles via spiroaziridines, as only a few examples of spiro-*N*-phthalimidoaziridines have been reported to date, and they have never been explored in 1,3-dipolar cycloaddition.[8,19–21] The conventional route for the preparation of *N*-phthalimidoaziridines is via addition of phthalimidonitrene to a >C=C< bond.[22] We chose 2-arylideneinden-1,3-diones **3** as precursors as they would provide a facile access to the desired spiroaziridines.[23] Additionally, the *para*-substituted aromatic ring allows evaluation of the substituent effect on the stability and activity of the corresponding intermediate azomethine ylides (vide infra).

The starting arylideneindendiones **3a–c** were obtained from diethyl phthalate (**1**) according to the literature method (Scheme 1).[24] This strategy includes in situ generation of inden-1,3-dione and serves as a convenient alternative to known methods for arylideneindendione preparation.[25–29] A slightly modified standard procedure[4,30] for the oxidation of *N*-aminophthalimide with $Pb(OAc)_4$ in the presence of unsaturated substrates **3a–c** gave aziridines **4a–c** (Scheme 1). Compounds **4a**,**b** gradually decomposed in air at room temperature, but they could be stored in a refrigerator for several months without decomposition. Our attempts to isolate the aziridine **4c** were unsuccessful, but its formation was invoked from subsequent transformations (see below). According to their ^{1}H NMR spectra, aziridines **4a**,**b** exist as single invertomers with *anti*-orientation of the aryl and phthalimide moieties, similar to other trisubstituted aziridines described previously.[4,5] Slow rotation of the phthalimide group around the N–N bond in sterically crowded molecules **4a**,**b** (as well as in most of the compounds reported below) led to broadening of its signals allowing the proton signals of two similar moieties (PhthN and the indendione

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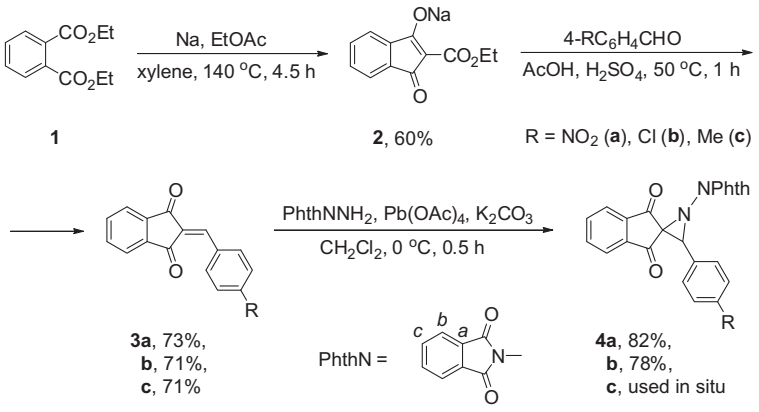


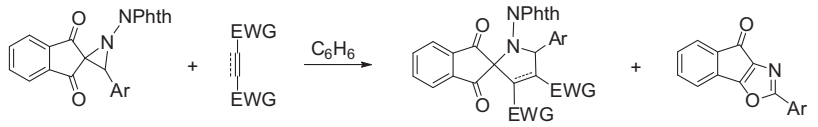
Scheme 1. Synthesis of aziridines **4a–c**.

fragment) to be distinguished in the ^{1}H NMR spectra of these aziridines. In line with this, the broadening or disappearance of CON and C^a signals was clearly evident in the ^{13}C NMR spectra.

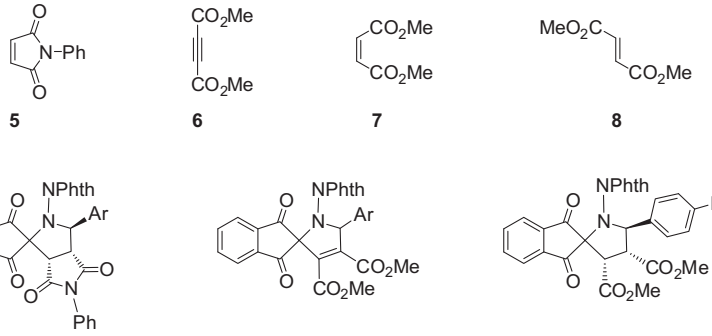
To evaluate the activity of spiroaziridines **4a–c** in 1,3-dipolar cycloaddition reactions, conventional dipolarophiles such as *N*-phenylmaleimide (**5**), dimethyl acetylenedicarboxylate (DMAD) (**6**), maleate **7**, and fumarate **8** were chosen (Table 1). Optimal conditions were found using ^{1}H NMR spectroscopy and TLC monitoring of the reaction mixtures with gradual increases in the temperature from 25 °C in ~15 °C/30 min increments.

The best results were achieved in the reactions with *N*-phenylmaleimide (**5**) in which all the expected cycloaddition products **9a–c** were isolated (Table 1, entries 1, 5 and 9). In many cases tricyclic oxazoles **12a**,**b** were obtained along with the corresponding

Table 1
Reactions of aziridines **4a–c** with dipolarophiles **5–8**



Ar = 4-$O_2NC_6H_4$ (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**)



Entry	Aziridine	Dipolarophile	*T* (°C)	Time (h)	Adduct	Yield[b] (%)	Oxazole	Yield[b] (%)
1	**4a**	**5**	75	8	**9a**	87	–	–
2	**4a**	**6**	75	8	**10a**	66	**12a**	5
3	**4a**	**7**	75	8	**11**	25	**12a**	30
4	**4a**	**8**	75	8	–	–	**12a**	60
5	**4b**	**5**	55	9	**9b**	95	–	–
6	**4b**	**6**	55	9	**10b**	77	**12b**	14
7	**4b**	**7**	55	9	–	–	**12b**	28
8	**4b**	**8**	55	9	–	–	**12b**	37
9	**4c**[a]	**5**	25	36	**9c**	34	–	–
10	**4c**[a]	**6–8**	25	36	–	–	–	–

[a] Used in situ.
[b] Isolated yield.

cycloadducts. Moreover, they were the only products in reactions with the least active dipolarophile – dimethyl fumarate (**8**) (Table 1, entries 4 and 8). Compounds **12a**,**b** are orange solids, which were poorly soluble in common organic solvents, and they usually precipitated from benzene during the course of the reaction.

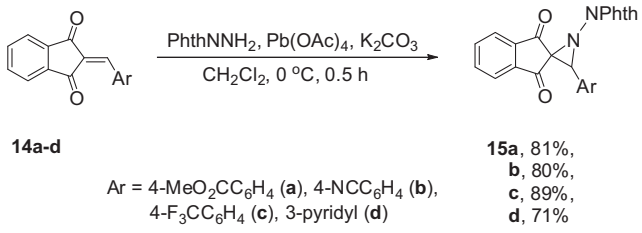
As mentioned above, all our attempts to isolate aziridine **4c** were unsuccessful and therefore we decided to add dipolarophiles to the filtered reaction mixture immediately after oxidative aminoaziridination of 2-(4-methylbenzylidene)-1*H*-indene-1,3(2*H*)-dione (**3c**). As a result, with *N*-phenylmaleimide (**5**) (2 equiv) after 1.5 days at room temperature, a precipitate formed which after purification was identified as adduct **9c** (Table 1). For other dipolarophiles **6**–**8**, TLC monitoring of the reaction mixtures showed disappearance of the spot that we tentatively assigned to the initial aziridine **4c** and formation of one new compound (orange spot with R_f = 0.25 (SiO_2, CH_2Cl_2)). However, our attempts to isolate this product by crystallization or column chromatography failed. It does not appear to be a cycloaddition product or an oxazole, since such instability would not be expected by replacement of NO_2 or Cl substituents in stable analogues by a methyl group. We speculate that decomposition of the three-membered ring occurs. The aziridine fragment in compounds **4a**–**c** is a part of a spirosystem where two substituents on one carbon atom are strongly bonded with each other. The 'spiroactivation' effect that appeared, for example, in apparently much easier ring cleavage of spiro-1,1-diacylcyclopropanes than that of their monocyclic analogues,[31,32] may have an analogous influence on the stability of aziridines **4a**–**c** as well. Cleavage of the C–N bond followed by destruction of the whole cycle may begin to dominate over concerted C–C cleavage in the sequence **4a** → **b** → **c** that may cause a decrease in yield, and even disappearance of cycloaddition products (Table 1, entry 10).

The pyrrolidine protons in adducts **9a**–**c** and **11** form simple ABX systems, but it is well known that the values of their vicinal coupling constants do not serve as unequivocal evidence of their spatial relations.[33] Therefore we used 2D ^{1}H NOESY to confirm the *trans*-orientation of the former aziridine proton and the protons of dipolarophile in the pyrrolidine ring of these compounds (Table 1), which corresponds to the less sterically strained configuration of these products. In the ^{1}H NMR spectra of compounds **10a**,**b** the signals of the ring protons were observed as singlets at 6.97 and 6.86 ppm, respectively, which is consistent with the structure of a 3-pyrroline, but not a 2-pyrroline.

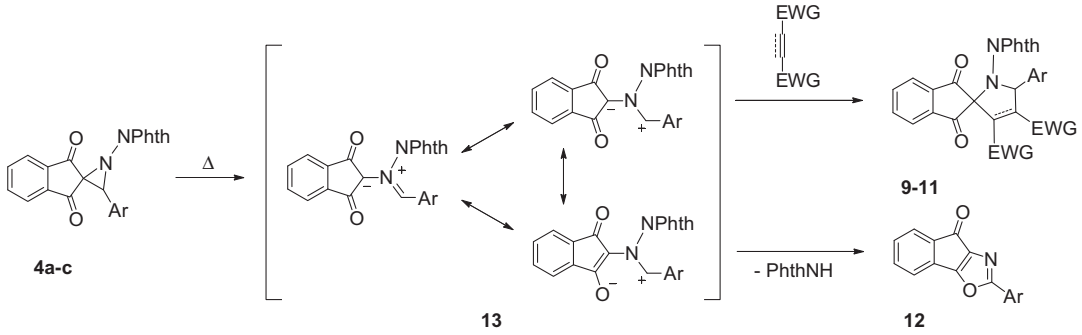
Thus, the structures of all adducts **9**–**11** are in accordance with a concerted mechanism of 1,3-dipolar cycloaddition of azomethine ylides **13**, generated thermally from aziridines **4a**–**c**, to the dipolarophile (Scheme 2). These results are in agreement with our previous findings on the chemistry of *N*-phthalimidoaziridines.[4,6,7] Oxazoles **12a**,**b** originate from 1,5-dipolar electrocyclization of the intermediate azomethine ylide **13** facilitated by the unavoidable proximity of any of the two keto groups to the terminal carbon atom of the 1,3-dipole; this is a known process for 2-acyl-substituted *N*-phthalimidoaziridines.[4,34] The decrease in dipolarophile activity in the sequence **5** → **8** disfavors 1,3-dipolar cycloaddition and gives oxazoles preferentially (Table 1). This is in agreement with the fact that the activation barrier for the cycloaddition depends on both the ylide and dipolarophile structures. In the presence of less active ylide 'traps', various intramolecular processes come into play and their rates depend primarily on the aziridine substituents.[35] Among them, 1,5-electrocyclization is obviously favorable because the required *s*-*cis*-orientation of an acyl substituent and terminal ylide carbon atom is inherent to ylides **13** (Scheme 2).

Less electron-withdrawing groups at the *para*-position in aziridines **4a**–**c** not only lead to milder reaction conditions for the cycloaddition (75 °C for NO_2 group, 55 °C—Cl, 25 °C—CH_3), but also to increased instability of the aziridine ring (aziridine **4c**, Table 1, entry 10). A similar dependence was also observed for 2,3-disubstituted *N*-phthalimidoaziridines[36] so it proves in general that push–pull aziridines with substituents of opposite electronic character on neighboring carbon atoms form azomethine ylides easier than those possessing only electron-withdrawing groups. While this phenomenon has already been explored to increase the reactivity of donor-acceptor substituted cyclopropane rings toward cycloaddition,[37,38] to the best of our knowledge, this is the first demonstration of analogous effects in aziridine scaffolds (compare[6,7]).

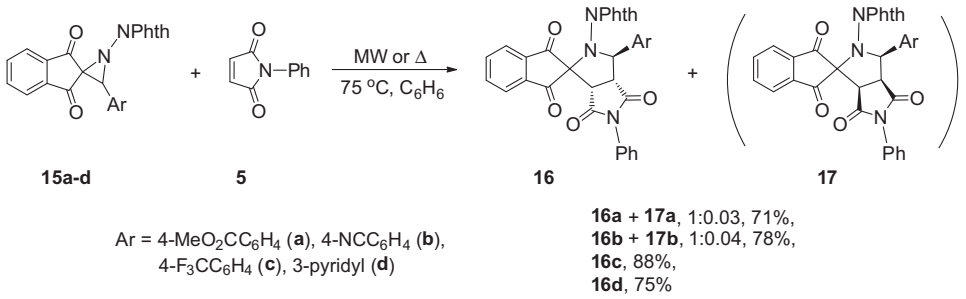
Since more stable spiroaziridines were obtained with electron-withdrawing substituents, for practical reasons, we decided to focus on these when extending the substrate scope. Thus, we prepared four additional *N*-phthalimidoaziridines **15a**–**d** possessing diverse electron-withdrawing groups on the aryl ring, including a 3-pyridyl moiety (Scheme 3). The starting arylideneindendiones **14a**–**d** were synthesized in 69–73% yields from salt **2** in the same manner as for the aforementioned substrates (Scheme 1), with the exception of 3-pyridyl-substituted compound **14d** where basic conditions were more suitable (see the Experimental section for details). Oxidative addition of *N*-aminophthalimide readily gave target aziridines **15a**–**d**.



Scheme 3. Preparation of aziridines **15a**–**d**.



Scheme 2. Plausible mechanisms for the formation of adducts **9**–**11** and oxazoles **12**.



Scheme 4. Reaction of aziridines **15a–d** with *N*-phenylmaleimide **5** (isolated yields and ratios are given for reactions under MW irradiation for 1.5 h).

As *N*-phenylmaleimide (**5**) provided the highest product yields among the dipolarophiles tested, we focused on it here as well. In order to convert aziridines **15a–d** into the expected cycloadducts, we used the same temperature as for the nitro-substituted compound **4a** (75 °C), but the use of microwave irradiation allowed for reduced reaction time (1.5 h, Scheme 4). This shorter microwave heating improved slightly the isolated yields. Formation of the corresponding oxazoles of type **12** was not observed, similar to the cases presented above (Table 1, entries 1, 5 and 9).

For aziridines **15a**,**b**, mixtures of two isomers **16a**/**17a** and **16b**/**17b** were obtained in the ratio ca. 1:0.035 (the reaction of aziridine **15c** under conventional heating also gave two isomers **16c**/**17c** in the ratio ca. 1:0.12), but all our attempts to separate these isomeric mixtures and to isolate the minor product using crystallization and column chromatography were not successful. The pyrrolidine proton signals of the ABX system in the major isomers **16a–d** have similar chemical shifts and coupling constant values as those for adducts **9a–c**, which proves the same spatial configuration (Scheme 4). In addition, the structure of compound **16d** was unambiguously confirmed by X-ray analysis (Fig. 1).[39] The *trans*-orientation of the former dipolarophile fragment and pyridine-substituent is evident from the value of the dihedral angle C(29)–C(6)–C(2)–C(3) 101.9(2)°. In the central pyrrolidine ring the bond lengths C(5)–C(1), C(6)–C(2) and N(2)–C(5), N(2)–C(6) are equal in pairs, while the valence angles are different. The smallest is the angle N(2)–C(5)–C(1) (98.14(17)°) that corresponds to the central position in the spiro-system. The central pyrrolidine ring has a slightly deflected '*envelope*' conformation with the dihedral angle C(5)–C(1)–C(2)–C(6) of −7.1(2)°.

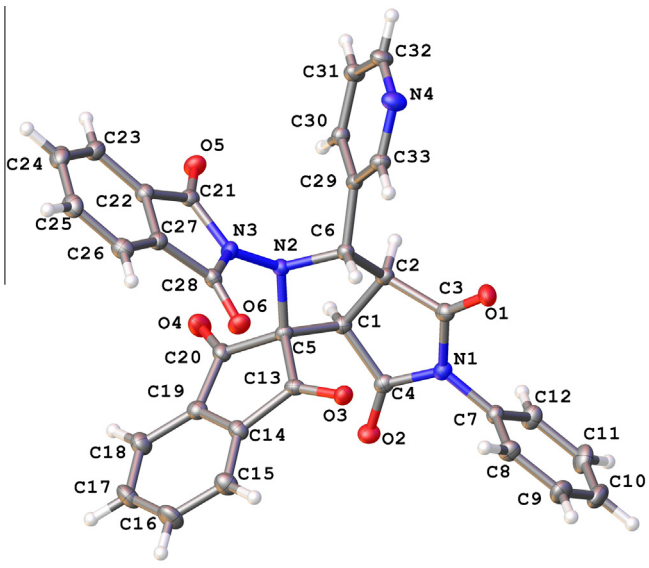


Figure 1. X-ray structure of adduct **16d**.

Table 2
Characteristic proton signals in the ^{1}H NMR spectra of isomeric adducts **16** and **17** ($CDCl_3$, 400 MHz)

Isomer	δ ($H^{3'}$), ppm	δ ($H^{3a'}$), ppm	δ ($H^{6a'}$), ppm
16	6.16–6.22 d (J = 7.3–7.5 Hz)	3.80–3.88 dd (J = 10.2, 7.3–7.5 Hz)	4.32–4.35 d (J = 10.2 Hz)
17	5.57–5.61 d (J = 7.6–7.9 Hz)	3.92–3.95 dd (J = 7.6–7.9 Hz)	3.67–3.68 d (J = 7.8–7.9 Hz)

Since we failed to isolate the minor isomers **17**, their structures are speculative. A comparison of the characteristic proton signals of the two isomers in the area 3.5–6.5 ppm shows that the minor species also have a pyrrolidine ring (minor proton signals in the aromatic area of the spectrum are barely separated from those of the main isomer) (Table 2). Obviously, the two protons of the former *N*-phenylmaleimide cannot be in *trans*-orientation and therefore the minor adducts appear to have all-*cis*-configuration (Scheme 4). A comparison of the magnitudes of the NOE in the 2D ^{1}H NOESY spectrum of the mixture of two isomers **16c**/**17c** confirms this assumption. The all-*cis*-structure is significantly more strained, which explains the very small amounts of minor isomers and high stereoselectivity of the process as a whole.

In conclusion, we have synthesized a series of novel highly functionalized spiro-fused *N*-phthalimidoaziridines. Depending on the substituents, these compounds feature different stability and reactivity as a result of strain in the system and the electronic properties for push–pull aziridines. The introduction of electron-withdrawing groups provides increased stability to the aziridines and enables their isolation and subsequent transformations. Azomethine ylides generated thermally from spiroaziridines in the presence of *N*-phenylmaleimide readily furnish products of 1,3-dipolar cycloaddition with very high stereoselectivity. Such spiro-fused heterocycles are difficult to obtain by other methods and therefore the described transformations may serve as a convenient method for their synthesis.

Acknowledgments

We are indebted to Prof. Khidmet S. Shikhaliev (Voronezh State University) for providing samples of compounds **3a–c** for our preliminary experiments and for his valuable advice on their synthesis. The authors thank Saint Petersburg State University for financial support (research grant number 12.38.16.2011) and the X-ray Diffraction Centre, Center for chemical analysis and materials research and Center for Magnetic Resonance of Saint Petersburg State University for XRD, MS and NMR studies, respectively.

Supplementary data

Supplementary data (Representative experimental details, characterization data for compounds, copies of the ^{1}H and ^{13}C NMR

spectra for compounds **2**, **4a**,**b**, **9a**–**c**, **10a**,**b**, **11**, **12b**, **14a**–**d**, **15a**–**d**, **16**/**17a**,**b**, **16c**,**d** and copies of the 2D ^{1}H NOESY spectra for compounds **9a**,**c**, **11**, **16c**/**17c**, **16d**.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.014.

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39. CCDC-968896 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.