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Publication Date	21 März 2022
Article Type	Letter
Supporting Information File 1	Vepreva ESI.pdf; 4.3 MB
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Unusual Highly Diastereoselective Rh(II)-catalyzed Dimerization of Diazo Arylidene Succinimides Provides Access to New Dibenzazulene Scaffold

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Abstract

Formation of unusual unsymmetrical dimers or/and indenes *via* $Rh_2(esp)_2$-catalyzed decomposition of diazo arylidene succinimides has been investigated. The reaction proceeded under mild conditions, and its result was shown to strongly depend on the nature of the substituents in the diazo substrate. The new reaction provides access to dibenzoazulenodipyrrole and indenopyrrole derivatives in moderate to high yield. Dibenzoazulenodipyrroles bearing alkyl substituents at the nitrogen atom showed pronounced cytotoxocity against A549 human lung adenocarcinoma cell line while *N*-aryl analogs were non-cytotoxic.

Introduction

3-Diazo-2-arylidene succinimides (DAS, **1**) are heterocyclic vinyl-substituted diazocarbonyl compounds with exclusively (*E*)-configured double bond which positions the aryl substituent and the diazo group in close proximity. The reactivity of DAS is twofold: on the one hand, these compounds undergo reactions which are typical for diazocarbonyl compounds, on the other hand, their specific geometry enables intriguing transformations with simultaneous involvement of the diazo function and the benzylidene fragment.

DAS were first described in 2020 and were involved in a [2+1] cycloaddition to aldehydes to give oxiranes [1]. Later on, we developed a convenient method for the preparation of this class of compounds [2] and showed that DAS can undergo Rh(II)-catalyzed insertion reactions into the heteroatom-H bonds [3]. In 2020, it was shown that under Rh(II) catalysis, DAS can enter insertion reactions into the C-O bond of ethers [4], a rare transformation for diazocarbonyl compounds [5]. The close spatial arrangement of the conjugate aryl fragment and the diazo group in the DAS molecule favors both intramolecular and intermolecular cyclizations involving the arylidene group. Thus, under catalytic decomposition, DAS containing a 2-pyridyl or 2-hydroxyaryl substituent at the double bond

underwent cyclization as the result of intramolecular interception of the rhodium carbene, which led to the formation of indolizine [6] or 2*H*-chromene [7] derivatives, respectively (Figure 1). At the same time, $Rh_2(esp)_2$-catalyzed reactions of DAS with nitriles and carbonyl compounds (aldehydes and ketones) enable to obtain the products of formal [5+2] cycloaddition reactions – 2-benzazepines [8] and 2-benzoxepines [9-10]. When studying the Rh(II)-catalyzed reaction of DAS with ketones [10], we attempted to involve poorly reactive fluorenone in the reaction. To our surprise, the formation of the spirocyclic benzoxepine was not observed. Instead, the principal product of the reaction was compound **2**, presumably resulting from the dimerization of the DAS molecule (Figure 1). Intrigued by this unexpected course of the reaction and also by the unusual structure of **2**, we set off to study this transformation. Herein, we present the results obtained in the course of this investigation.

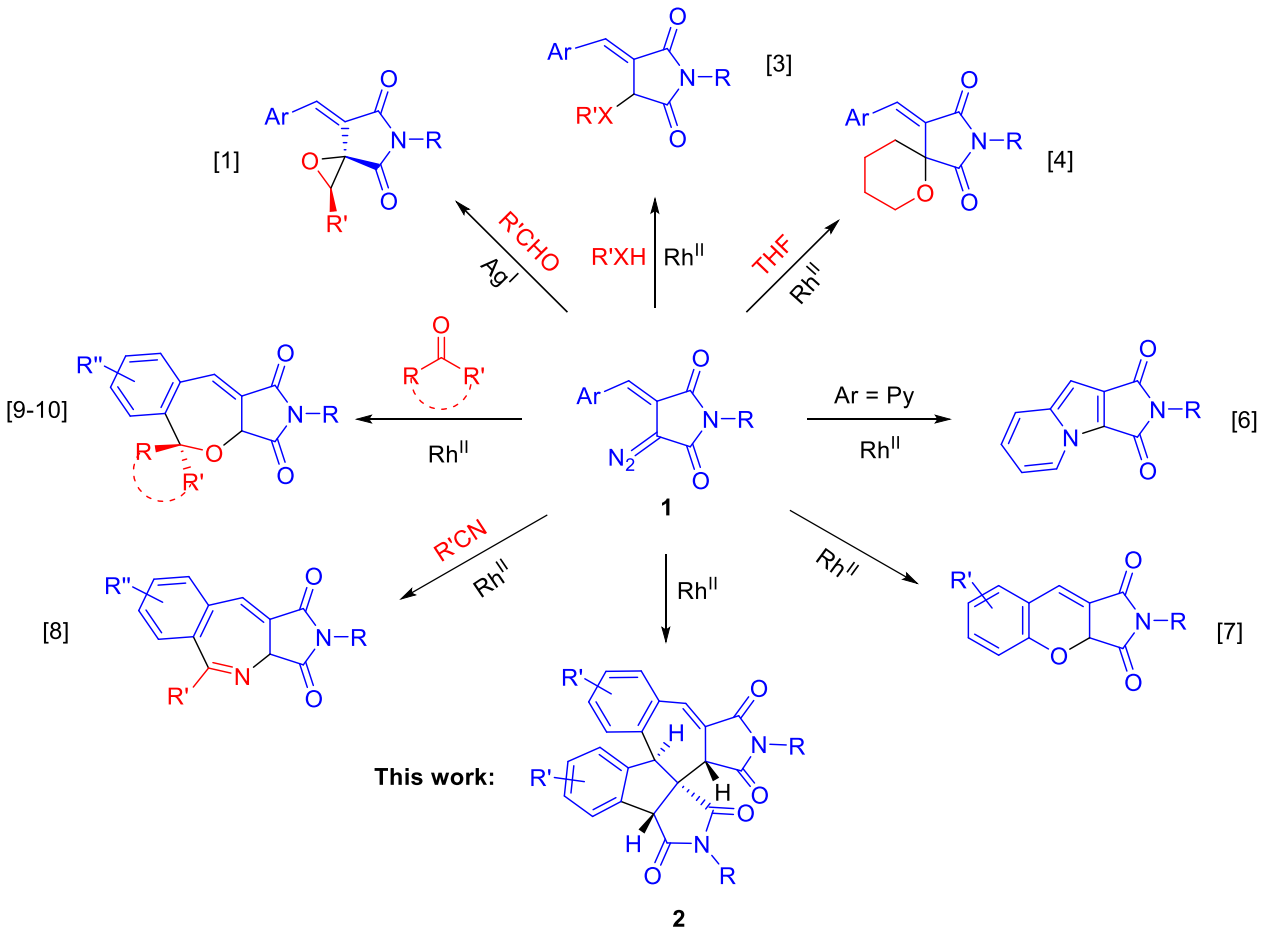


Figure 1. Previously reported transformations of DAS (**1**) and their unusual dimerization investigated in this work.

Results and Discussion

The decomposition reaction of DAS **1a** in dichloromethane in the presence of $Rh_2(esp)_2$ (0.1 mol%) led to the formation of a mixture of the major product – dimer **2a**, and minor indene **3a** (Table 1,

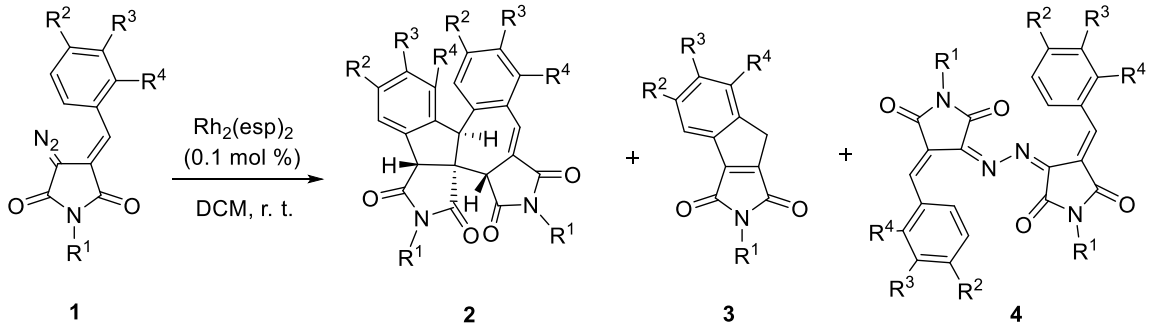
Entry 1). The target dimer was isolated in 74% yield as a single diastereomer. Its structure was reliably confirmed by the X-ray analysis data (see ESI). Given that the main product **2a** is most likely the result of a bimolecular process while indene **3a** was formed *via* an intramolecular transformation, we attempted to completely switch the direction of the reaction in order to achieve an indene to form as the main product. However, carrying out the reaction under tenfold dilution did not fully suppress the bimolecular process to give indene **3a** in an acceptable yield, although its content in the reaction mixture increased significantly (Table 1, Entry 1).

Next, we investigated the influence of substituents in the DAS component **1** on the outcome of their Rh(II)-catalyzed decomposition. The results obtained clearly demonstrate that the nature of the substituent at the nitrogen atom in the DAS molecule has a minor effect: the substrates bearing both donor- and acceptor-substituted aryl groups form dimers **2** in high yields (Table 1, Entries 2-5). In the case of *N*-benzyl substituted DAS, by-product azine **4** was detected by NMR analysis (Table 1, Entry 6). The formation of these by-products was also observed in the case of other DAS bearing alkyl groups at the nitrogen atom (Table 1, Entries 10-13) as well as in the case of DAS **1i** containing a trifluoromethyl group in the arylidene ring (Table 1, Entry 9). In the latter case, the negative effect of the presence of the electron-withdrawing group also manifested itself in a significant decrease in the yield of the target dimer **2** due to the formation of unidentified impurities. In one case, azine **4k** was isolated in pure form and characterized. It should be noted that such azines are typically observed as by-products in Rh(II)-catalyzed reactions of diazocarbonyl compounds [11].

The introduction of a strong donor substituent (MeO) in position 4 of the benzylidene fragment (**1b**) led to the deactivation of the diazo substrate – after 1 hour the conversion did not exceed 30%, and even after 3 days, the starting DAS **1b** was still present in the mixture. At the same time, only a trace amount of the expected dimerization product **2b** were detected along unidentified by-products.

For 3-methoxy substituted DAS **1n**, the main reaction outcome was the unimolecular cyclization, leading to a mixture of regioisomeric indenes (Table 1, Entry 14) while the target dimer **2n** was obtained in low (12%) yield. A similar result was obtained earlier in the study of DAS reaction with nitriles [8].

Table 1. Transformation of DAS **1** under Rh(II)-catalyzed decomposition.



1 **2** **3** **4**

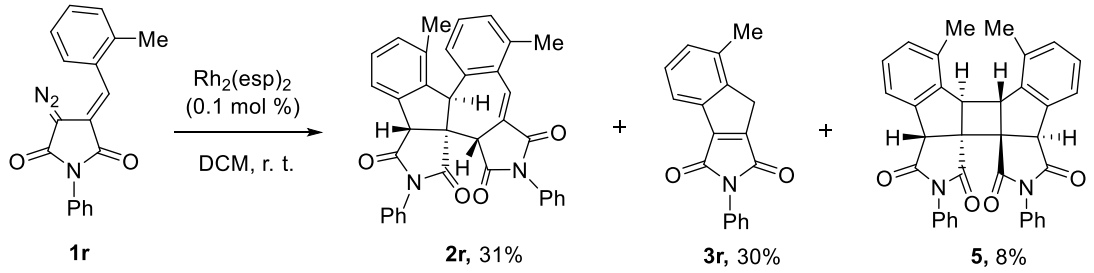
Entry	Compounds	R^1	R^2, R^3, R^4	Yield of **2**[a] (%)	Yield of **3** (%)	Yield of **4** (%)
1	**1/2/3/4a**	Ph	H, H, H	74 40[c]	(10)[b] 15[c] (42)	-
2	**1/2/3/4b**	4-$MeOC_6H_4$	H, H, H	73	-	-
3	**1/2/3/4c**	4-$CF_3C_6H_4$	H, H, H	74	(6)	-
4	**1/2/3/4d**	4-MeC_6H_4	H, H, H	63	(13)	-
5	**1/2/3/4e**	4-FC_6H_4	H, H, H	86	-	-
6	**1/2/3/4f**	Bn	H, H, H	68	(14)	(10)
7	**1/2/3/4g**	Ph	MeO, H, H	traces	-	-
8	**1/2/3/4h**	Ph	Me, H, H	93	-	-
9	**1/2/3/4i**	Ph	CF_3, H, H	18	-	(20)
10	**1/2/3/4j**	Ph	H, H, F	60	(12)	(18)
11	**1/2/3/4k**	Bn	F, H, H	42	-	13 (21)
12	**1/2/3/4l**	*c*Pr	F, H, H	43	-	(21)
13	**1/2/3/4m**	*i*Bu	Cl, H, H	52	(7)	(12)
14	**1/2/3/4n**	Ph	H, MeO, H	12	56 [d]	-
15	**1/2/3/4o**	2-ClC_6H_4	H, H, H	-	35	-
16	**1/2/3/4p**	2-MeO-5-ClC_6H_3	H, H, H	-	34	-
17	**1/2/3/4q**	2-$CO_2EtC_6H_4$	H, H, H	-	54	-

Reaction conditions: 0.25 M solution of DAS **1** in DCM; 0.5 or 1.0 mmol scale.
[a] Isolated yields.
[b] NMR yields are shown in parentheses.
[c] Reaction was run under tenfold dilution.
[d] 1.8:1.0 mixture of regioisomers was obtained (ratio 1.8:1).

An unexpected and interesting result was the exclusive formation indenes **3** during the catalytic decomposition of DAS containing an *ortho*-substituted phenyl group at a nitrogen atom (Table 1, Entries 15-17). In all three cases, compounds **3** were obtained in moderate yields, while the formation of the corresponding dimers **2** or azines **4** was not observed. Most likely, the introduction of the *ortho*-

substituent disturbed the molecule's coplanarity, which may have created steric obstacles for the intermolecular process.

Rather remarkable was the reaction of DAS **1r** containing an *ortho*-methyl substituent in the benzylidene fragment. In this case, along with conventional reaction products – dimer **2r** and indene **3r**, unexpected cyclobutane **5**, a product of the formal [2+2] cycloaddition, was isolated in low yield (Scheme 1); its structure was confirmed by the single-crystal X-ray analysis (see ESI).

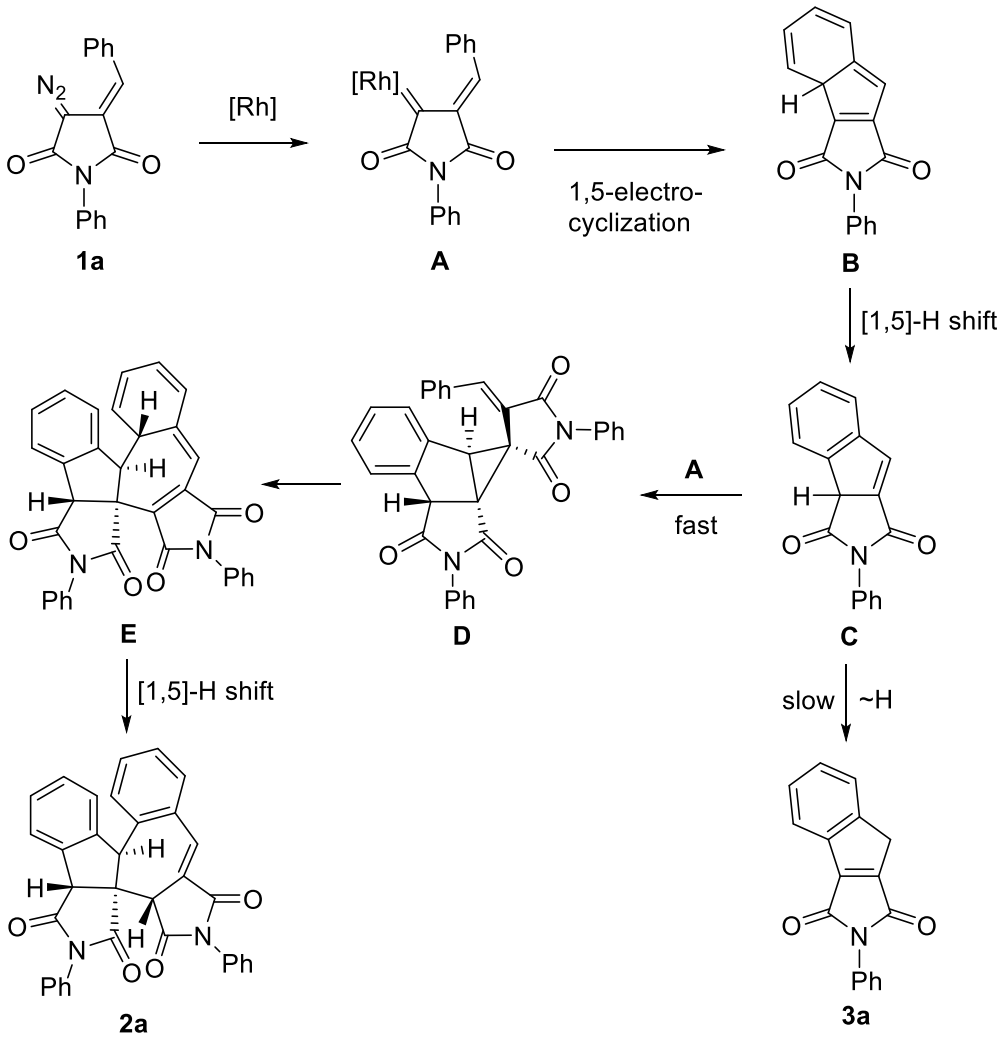


1r **2r**, 31% **3r**, 30% **5**, 8%

Scheme 1. The result of Rh(II)-catalyzed decomposition of DAS **1r**.

A plausible mechanism of the observed transformations of DAS (shown for **1a**) is presented in Scheme 2. The initially formed rhodium carbene **A** undergoes 1.5-electrocyclation to form intermediate **B** which turns into indene **C** as the result of 1,5-suprafacial hydrogen shift. Indene **C** can convert into the final indene **3a** *via* a slow 1,3-migration of the hydrogen atom, or be intercepted by carbene **A** with the formation of cyclopropane **D**. The relative rates of these competing processes likely determine the composition of the final product mixture. The formation of a single diastereomer at the cyclopropanation step can be explained by the preferred approach of carbene **A** from the least sterically hindered side of indene **C** and the π-stacking interaction of the aromatic fragment of indene and the benzylidene substituent of carbene.

The conversion of intermediate **D** into cycloheptadiene **E** is an example of a relatively rare reaction of the cyclopropane ring expansion through a 1,5-C–C bond migration [12]. This concerted process is followed by yet another 1,5-migration of the hydrogen atom, leading to the final dimer **2a**. The formation of a single diastereomer **2a** is indicative of a sequence of concerted processes with an unambiguous stereochemistry control at each step where stereogenic centers are formed.



Scheme 2. Plausible mechanism for the formation of dimer **2a** and indene **3a** on Rh(II)-catalyzed decomposition of **1a**.

Dibenzoazulenodipyrroles **2** have a pronounced three-dimensional character which make this chemotype promising probe for protein-protein interactions, including oncogenic ones [13]. As the first step towards biological characterization of compounds **2**, they were screened for cytotoxicity against A549 human lung adenocarcinoma cell line. Among the eleven compounds, *N*-aryl analogs **2a-e**, **2h** and **2j** had no effect on the cancer cell viability. However, *N*-alkyl analogs **2f** and **2k-m** showed a pronounced cytotoxicity with IC_{50} values in the single- to double-digit micromolar range (Figure 2).

Compound	IC_{50}, μM[a]
2f	6.38 ± 3.39
2k	23.84 ± 11.17
2l	16.64 ± 2.91
2m	2.58 ± 1.57

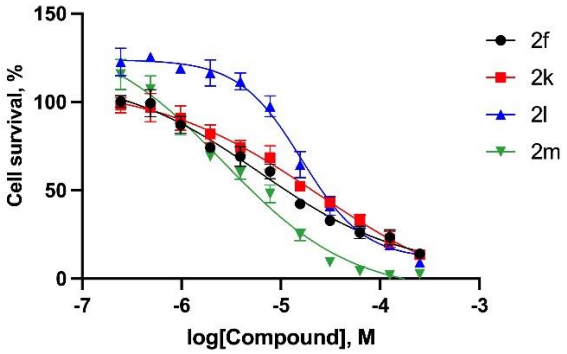


Figure 2. Cytotoxicity of *N*-alkyl substituted compounds dibenzoazulenodipyrroles **2** against A549 human lung adenocarcinoma cell line.

Conclusion

In summary, we have shown that the reaction triggered by the Rh(II)-catalyzed decomposition of DAS in inert medium can proceed in two principal directions and result in the formation of an unusual unsymmetrical dibenzoazulenodipyrrole dimer **2** and/or a product of intramolecular cyclization – indene **3**. The result of the reaction is determined by the nature of substituents in the starting DAS molecule. In most cases, dimers **2** were obtained as a single diastereomer in high yields. In some cases, indenes were obtained in moderate yields. A plausible mechanism of the observed transformations was proposed which implicates a rare rearrangement of the cyclopropane intermediate as the key step. Dimers **2** bearing alkyl substituents at the nitrogen atom showed pronounced cytotoxocity against A549 human lung adenocarcinoma cell line while *N*-aryl analogs were non-cytotoxic.

Supporting Information

Supporting Information File 1

General experimental information, X-ray crystallographic data, synthetic procedures, analytical data and NMR spectra for the reported compounds.

[https://www.beilstein-journals.org/bjoc/content/supplementary/xxxx-xxxx-xx-xx-S1.pdf]

Acknowledgements

We thank the Research Center for Magnetic Resonance, the Center for Chemical Analysis and Materials Research and the Center for X-ray Diffraction Methods of Saint Petersburg State University Research Park for obtaining the analytical data.

Funding

This research was supported by the Russian Science Foundation (project grant 20-13-00024).

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