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Triaryl-Substituted Divinyl Ketones Cyclization: Nazarov Reaction versus Friedel−Crafts Electrophilic Substitution

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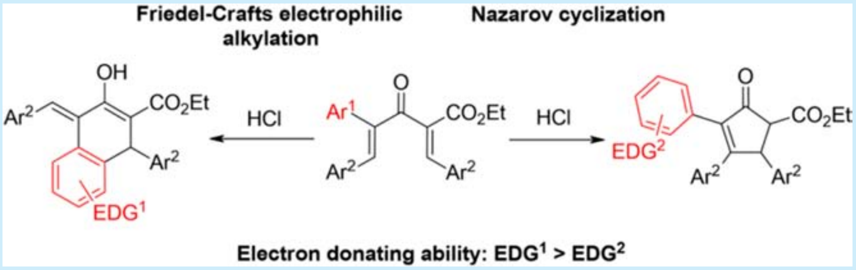
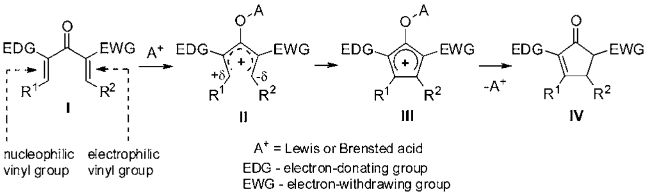
S *Supporting Information*



ABSTRACT: The acid-catalyzed cyclization of a wide range of triaryl-substituted divinyl ketones has been studied. It was found that the reaction pathway strongly depends on the nature of the aryl substituent at the α-position to the carbonyl group. An electron-rich aromatic substituent promotes the reaction to proceed through the intramolecular Friedel−Crafts electrophilic substitution giving dihydronaphthalene derivatives. In contrast, the presence of an electron-deficient substituent is favorable for the Nazarov 4π-conrotatory cyclization yielding triaryl-substituted cyclopentenones. The electrophilic substitution reaction was applied to thiophene and thiazole derivatives.

Divinyl ketones are important synthons for the synthesis of a wide range of complex compounds, including carbo- and heterocyclic systems.[1−6] The polyfunctional nature of these compounds makes them versatile participants in a variety of other reactions. These synthons were utilized in a number of reactions, including Diels−Alder,[2,7] Friedel−Crafts,[8] and Michael reactions with different nucleophiles.[3,4,9−12] The most popular reaction of divinyl ketones is the acid-catalyzed Nazarov cyclization producing cyclopentenone derivatives.[1,13] The first step of Nazarov cyclization involves the protonation of a carbonyl oxygen atom of **I**, resulting in the formation of pentadienyl intermediate **II**, followed by the cyclization to form **III** and the subsequent elimination of an acid moiety producing target cyclopentenone **IV** (Scheme 1).

Scheme 1. Nazarov Cyclization of Polarized Divinyl Ketones



The Nazarov reaction offers considerable potential in organic synthesis.[13−17] However, the main drawback of the classical Nazarov reaction is that it requires high quantities (one or more moles) of strong Lewis acids. It should also be noted that the protonation and proton elimination are not regioselective, resulting in a loss of stereoselectivity. These issues have been addressed by different research teams.[13a,b,14a,15b,18] In particular, Denmark et al. investigated the substituent effects on divinyl ketones and postulated that a cation-stabilizing substituent at the α-positions would stabilize the oxyallyl cation product, thus lowering the activation barrier for the cyclization.[13a,18,19] Frontier and co-workers have succeeded in facilitating the Nazarov cyclization by synthesizing polarized divinyl ketones (Scheme 1).[20] Polarized divinyl ketones were used by other research groups.[21−25] Recently, we have also utilized polarized triaryl-substituted divinyl ketones **I** (EWG = CO_2Et; EDG, R^1, R^2 = (hetero)aryl, Scheme 1) for the synthesis of photochromic diarylethenes of the cyclopentenone series.[26] In order to synthesize a single photochromic isomer containing a double bond between the aromatic substituents in the target cyclopentenone **IV**, the polarized divinyl ketones have been

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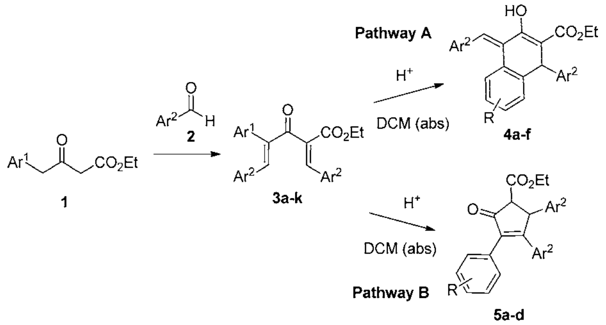
prepared by the introduction of the ester fragment as an electron-withdrawing group.

In the framework of our research on the development of new efficient methods for the synthesis of photoswitch materials[27] and biologically active compounds,[28,29] we have continued studying the Nazarov reaction. The aim of the present research is the study of the cyclization of divinyl ketones to probe the boundaries of the selectivity between the Nazarov cyclization and the electrophilic substitution.

Key triaryl-divinyl ketones **3** were prepared in 41–94% yields from aryl(hetaryl) derivatives of ethyl 4-aryl-3-ketobutanoate **1** using a known procedure (Scheme 2, Table 1).[22,23,26,30,31]

Scheme 2. Synthesis and Cyclization of the Divinyl Ketones



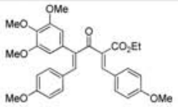
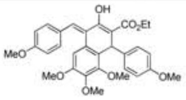
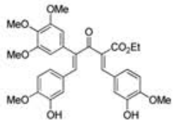
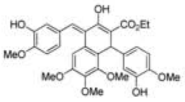
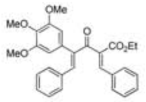
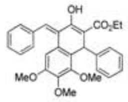
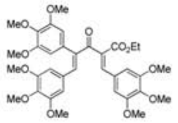
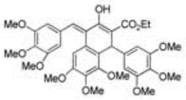
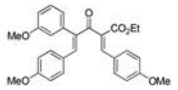
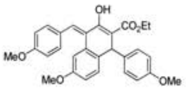
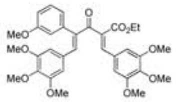
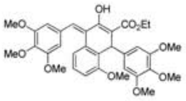
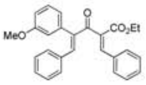
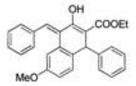
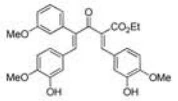
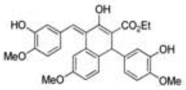
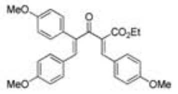
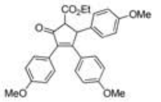
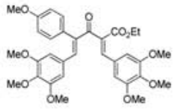
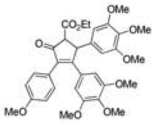
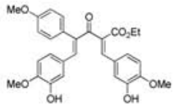
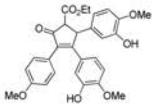
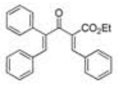
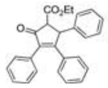
Depending on the nature of the Ar^1-substituent, the reaction was found to proceed by either the classical Nazarov reaction or the intramolecular Friedel–Crafts alkylation. If the *ortho*-position of the Ar^1-substituent is activated (**3a–h**, entries 1–8 in Table 1), the reaction produced dihdyronaphthalene derivatives **4**. Phenyl or 4-methoxyphenyl derivatives, in which the *ortho*-position is inactivated (**3i–l**), underwent the classical Nazarov cyclization giving cyclopentenone **5** as the only product.

To the best of our knowledge intramolecular Friedel–Crafts electrophilic substitution of divinyl ketones is unknown. Intramolecular Friedel–Crafts electrophilic substitution of aryl monovinyl ketones,[32] cinnamoyl derivatives of indole,[33] and a tandem double intermolecular Friedel–Crafts reaction of divinyl ketones[8a] have been described.

Interesting results were obtained with the use a 3-methoxyphenyl moiety as an aryl substituent at the α-position to the carbonyl group (**3e–h**, entries 5–8 in Table 1). In this case, the electrophilic substitution can occur at either the *ortho*- or *para*-position with respect to the methoxy group. An analysis of the ^{1}H NMR spectra provides unambiguous evidence that the electrophilic substitution in compounds containing the 3,4,5-trimethoxyphenyl moiety as the β-substituent occurs at the *ortho*-position (entry 6 in Table 1), whereas *para*-substituted products are generated in two other cases (entries 5, 7, 8 in Table 1). The reaction pathway observed in the case of the 3,4,5-trimethoxyphenyl derivatives is likely due to steric hindrance.

Further investigations showed that the nature of the catalyst has no effect on the pathway of the cyclization reaction of triaryl-substituted divinyl ketones; however, the reaction rate and yields of the final products strongly depend on the nature of the protonating agent. We recently reported that among various acid catalysts tested ($TiCl_4$, $SnCl_4$, HCl, $BF_3{\cdot}Et_2O$, and CF_3COOH) the hydrogen chloride (gas) and the tin(IV) chloride performed best in promoting the cyclization.[26]

Table 1. Structures of the Starting Divinyl Ketones and Products of the Acid-Catalyzed Reaction

entry	No	starting divinyl ketone **3**	products **4** or **5**	yields,[a] % HCl ($SnCl_4$)
1	3a/ 4a			45 (25)
2	3b/ 4b			80 (45)
3	3c/ 4c			65 (-)
4	3d/ 4d			82 (52)
5	3e/ 4e			81 (-)
6	3f/ 4f			52 (-)
7	3g/ 4g			76 (-)
8	3h/ 4h			40 (-)
9	3i/ 5a			90 (84)
10	3j/ 5b			80 (63)
11	3k/ 5c			85 (74)
12	3l/ 5d			96 (-)

[a] The yields are given for products isolated by column chromatography.

Therefore, in this study, we examined only these two catalysts. As can be seen in Table 1, isolated yields ranging from 45% to 96% were obtained with the use of hydrogen chloride, whereas, in the case of $SnCl_4$, the yields were much lower.

To clarify the yields for some compounds (**3a,f,h**) when using HCl_g as the catalyst, which have been isolated with average yields, the NMR monitoring was performed (Figure 1). It should be noted that the divinyl ketones **3** containing electron-rich substituents at the α-position to the carbonyl

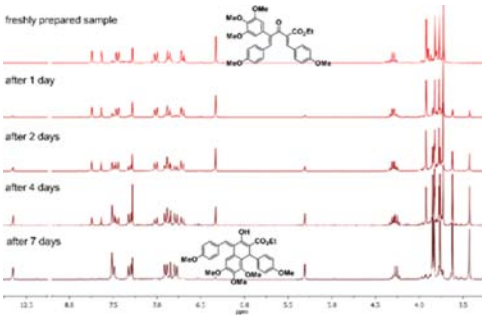


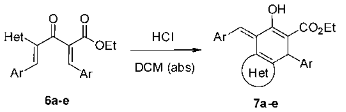
Figure 1. ^{1}H NMR monitoring of the reaction of divinyl ketone **3a** in $CDCl_3$ catalyzed by acid traces (in the dark, at ambient temperature).

group exhibited extremely high sensitivity toward hydrogen chloride. Therefore, the reaction has been carried out in $CDCl_3$ as solvent without additional HCl(g). It was found that the reaction of these compounds also proceeds smoothly, but isolated yields were lower probably due to instability.

As can be seen in Figure 1, the divinyl ketone was completely converted into dihydronaphthalene **4a** in the dark within 7 days. Apparently, the reaction is catalyzed by impurities of DCl and/or HCl. In the final product, deuterium is replaced by hydrogen due to the presence of a water impurity in the solvent.

This transformation has also been extended to the derivatives of thiophene and thiazole. Dihydro derivatives of benzothiophene **7a−d** and benzothiazole **7e** were synthesized by the cyclization of thiophene- and thiazole-containing divinyl ketones **6a−e** in good yields (Scheme 3, Table 2).

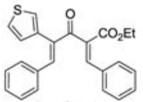
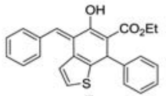
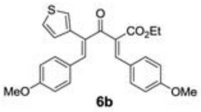
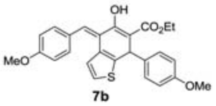
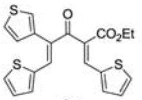
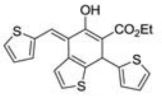
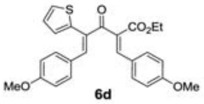
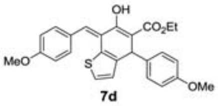
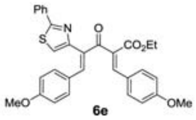
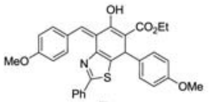
Scheme 3. Synthesis of Divinyl Ketones Bearing Heterocycle Moieties



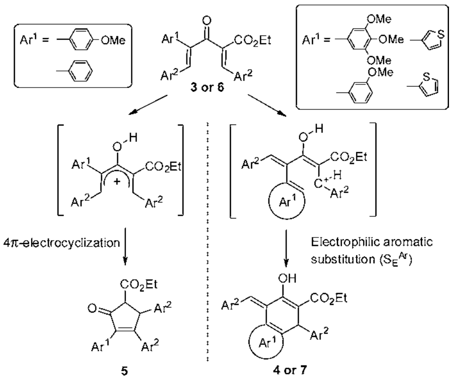
The structures of the products obtained on acid-catalyzed cyclizations of divinyl ketones were established by ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry. For three target products (**4d**, **4h**, **7b**), the complete assignment of the NMR signals was performed using 2D NMR techniques (for details see Supporting Information). The structure of compound **4c** was proven by X-ray.[34] The results of these studies unambiguously confirmed the *E*-configuration at the double bond, which is a consequence of the *cis* configuration of the aromatic substituents at the double bond in the starting divinyl ketones.

The proposed mechanism of these transformations is shown in Scheme 4. The difference in the reactivity of divinyl ketones **3** is attributed mainly to the nature of the aromatic substituent Ar^1 at the *α*-position to the carbonyl group. The first step involves the protonation of the carbonyl group giving the appropriate cation. The further reaction pathway is dictated by the nature of the substituent. The presence of substituents with the activated *ortho*-position (3,4,5-trimethoxyphenyl, 3-methoxyphenyl *α*- and *β*-thienyl) facilitates the intramolecular Friedel−Crafts alkylation giving rise to compounds **4**. Divinyl ketones, which contain phenyl and *para*-methoxyphenyl substituents and are inactivated at the *ortho*-position, generate standard Nazarov reaction products **5**.

Table 2. Annulation of Heterocycles by Intramolecular Alkylation

entry	starting divinyl ketone **6**	products (isolated yields) **7**	yields, %
1	 **6a**	 **7a**	67
2	 **6b**	 **7b**	74
3	 **6c**	 **7c**	78
4	 **6d**	 **7d**	55
5	 **6e**	 **7e**	63

Scheme 4. Proposed Mechanism of Acid-Catalyzed Reactions of Divinyl Ketones



According to the proposed mechanism, the reaction pathways may depend not only on *α*- but also *β*-substituents. In the future in order to establish the scope and limitations of these transformations, we plan to investigate the effect of these substituents on the reaction pathways by using the quantum chemical calculations and experimental methods. This may become extremely useful in the areas of dihydronaphthalene and cyclopentenone. It should also be noted that the aromatization/isomerization transformation reaction of the dihydro-naphthalene[35] opens a new avenue for the future study and application of this reaction. Additionally, the dihydronaphthalene derivatives show various biological activities,[36] so the development of efficient methods for their synthesis is highly relevant.

To conclude, we have studied acid-catalyzed cyclization of triaryl-substituted divinyl ketones. It was found that the cyclization of polarized divinyl ketones strongly depends on the nature of the aryl moiety at the *α*-position with respect to the carbonyl group. An electron-rich aromatic substituent facilitates the intramolecular electrophilic substitution, while the presence of an electron-deficient substituent is favorable for the Nazarov reaction yielding triaryl-substituted cyclopentenones. The electrophilic substitution reaction was applied to divinyl ketones based on thiophene and thiazole derivatives, resulting in the preparation of dihydro derivatives of benzothiophene and benzothiazole in good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03023.

Experimental procedures and full spectroscopic data for all new compounds (PDF)

Crystallographic file for compound **2c** (CIF)

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Notes

The authors declare no competing financial interest.

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