Tandem Nazarov cyclization–halovinylation of divinyl ketones under Vilsmeier conditions: synthesis of highly substituted cyclopentadienes†

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Received (in Cambridge, UK) 27th August 2009, Accepted 27th November 2009
First published as an Advance Article on the web 13th January 2010
DOI: 10.1039/b917703e

A new Vilsmeier reagent-mediated Nazarov cyclization–halovinylation reaction of divinyl ketones was developed to provide a straightforward method for the synthesis of highly substituted cyclopentadienes with the advantages of simplicity of execution, readily available substrates, cheap reagents, and broad range of potential products and applications.

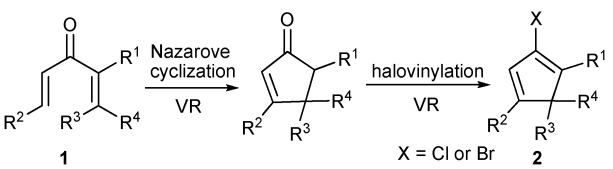
Cyclopentadienes (Cps) are members of a diverse class of fascinating molecules with wide potential in organic and organometallic chemistry. New and straightforward methods to access these substrates are therefore always highly desirable; in particular, an approach for highly substituted Cps remains a great challenge to synthetic chemists.[1,2] In this communication, a new route for the direct synthesis of highly substituted halocyclopentadienes (halo-Cps)[2g,h] is described based on an unusual type of Nazarov cyclization[3,4] and subsequent halovinylation of easily available divinyl ketones in a single step under Vilsmeier conditions.

The present study arose from our interest in developing the synthetic potential of α-alkenoyl ketene dithioacetals **1** (Scheme 1, $R^3 = R^4 = SR$), the divinyl ketones with terminal *gem*-dialkylthio substituents.[5,6] On the basis of previous reports on the reactions of **1** with Vilsmeier reagents (VRs),[6] we envisioned that **1** may be suitable precursors for the straightforward preparation of halo-Cps **2** if the Nazarov cyclization, a powerful tool for the construction of 2-cyclopentenones from divinyl ketones,[3,4] can be initiated by VRs[7] and followed by an extra halovinylation step[7] (Scheme 1). Fortunately, the above designed procedure was successfully achieved and presented several new chemistries: (1) a new promoter (VRs) for Nazarov cyclization was used;[3,4] (2) an unusual "interrupted" Nazarov cyclization was reported to undergo a Nazarov cyclization followed by an extra halovinylation involving an unconventional enol trapping;[3] (3) the products obtained were polysubstituted halocyclopentadienes, a structure type never before associated with the Nazarov cyclization,[3,4] and thus, (4) a new and straightforward strategy for cyclopentadiene synthesis from divinyl ketones was established.

To understand the role of Vilsmeier reagents in Nazarov cyclization, a model reaction of α-cinnamoyl-α-(4-methoxylphenyl) ketene dithioacetal **1a** (Table 1) was initially undertaken.‡ To our delight, a white solid, which was identified as chlorinated cyclopentadiene **2a**, was obtained in 10% isolated yield by treatment of **1a** (1.0 mmol) with $POCl_3$ (2.0 eq.) in 10 mL DMF at room temperature for 12 h. The transformation of **1a** to **2a** not only discloses the role of VR as a new promoter for Nazarov cyclization,[3,4] but also provides the first straightforward access to highly substituted Cps from divinyl ketones.[1,2,8] Thus, the optimization of the reaction conditions with respect to the amount of $POCl_3$ and DMF and the reaction temperature was performed carefully. The best result was obtained with 2.5 equiv. of $POCl_3$ (in 5.0 mL DMF) and reacted at 90 °C (entry 1).

Encouraged by the successful synthesis of Cp **2a**, a series of α-(4-methoxylphenyl) divinyl ketones **1a–g** were prepared to explore the scope of this new synthetic strategy under optimal conditions. Representative results are summarized in Table 1. In general, this reaction showed broad tolerance for aromatic R^2 substituents. Substrates **1a–f**, with either electron-neutral (entry 1), electron-rich (entries 2 and 3), or electron-deficient aryls (entries 4–6), afforded the corresponding Cps **2a–f** in good to high yields. In the case of **1g** with aliphatic R^2, a complex mixture was obtained (entry 7) even though the reaction was run at room temperature. Then, divinyl ketones **1** having an *o*-hindered aromatic R^1 (2-$MeOC_6H_4$) or electron-withdrawing aromatic R^1 (4-FC_6H_4) were examined. It was proved that the desired Cps **2g–k** could be obtained in good yields under the identical conditions by the reactions of the selected **1h–l** (entries 8–12). Furthermore, divinyl ketone **1m** having an alkyl substituent at α-position was also proven to be a suitable precursor and afforded Cp **2l** in 73% yield (entry 13). For significant comparison, however, substrate **1n** (with R^1 = PhCO) gave a complex mixture under identical conditions (entry 14).[9]

Next, PBr_3–DMF was used as the VR to evaluate the efficiency of the cyclization–bromovinylation of **1**. As shown in Table 1, entries 15–20, reactions of all selected substrates **1** also proceeded efficiently to give the corresponding brominated Cps **2m–r** in 76–85% yields, respectively. All halo-Cps **2a–r** obtained above were well-characterized by their spectra and analytical data and were further established by X-ray diffraction studies of **2f**.[10]



Scheme 1 Design of functionalized Cp synthesis.

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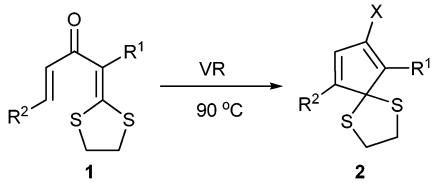
† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. CCDC 734569. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b917703e

Table 1 Synthesis of cyclopentadienes **2** from α-alkenoyl ketene dithioacetals **1** under Vilsmeier conditions[a]



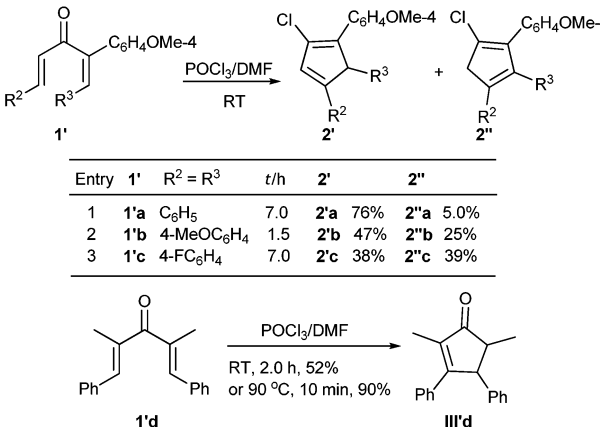
1 **2**

Entry	1	R^1	R^2	2	X	*t*/h	Yield (%)[b]
1	**1a**	4-$MeOC_6H_4$	C_6H_5	**2a**	Cl	2.0	86
2	**1b**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**2b**	Cl	0.5	79
3	**1c**	4-$MeOC_6H_4$	4-biphenyl	**2c**	Cl	1.0	80
4	**1d**	4-$MeOC_6H_4$	4-FC_6H_4	**2d**	Cl	1.5	78
5	**1e**	4-$MeOC_6H_4$	4-ClC_6H_4	**2e**	Cl	1.5	77
6	**1f**	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	**2f**	Cl	3.0	61
7	**1g**	4-$MeOC_6H_4$	*t*-Bu	—	—	5.0	—[c]
8	**1h**	2-$MeOC_6H_4$	C_6H_5	**2g**	Cl	3.0	74
9	**1i**	2-$MeOC_6H_4$	4-$MeOC_6H_4$	**2h**	Cl	1.5	67
10	**1j**	2-$MeOC_6H_4$	4-ClC_6H_4	**2i**	Cl	4.0	66
11	**1k**	4-FC_6H_4	C_6H_5	**2j**	Cl	4.5	46
12	**1l**	4-FC_6H_4	4-ClC_6H_4	**2k**	Cl	4.5	55
13	**1m**	Me	C_6H_5	**2l**	Cl	0.5	73
14	**1n**	C_6H_5CO	C_6H_5	—	—	3.0	—[c]
15	**1a**	4-$MeOC_6H_4$	C_6H_5	**2m**	Br	3.0	81
16	**1b**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**2n**	Br	3.0	84
17	**1d**	4-$MeOC_6H_4$	4-FC_6H_4	**2o**	Br	3.0	85
18	**1f**	4-$MeOC_6H_4$	4-$NO_2C_6H_4$	**2p**	Br	3.0	76
19[d]	**1h**	2-$MeOC_6H_4$	C_6H_5	**2q**	Br	3.5	77
20	**1m**	Me	C_6H_5	**2r**	Br	0.5	80

[a] Reagents and conditions: **1** (1.0 mmol), $POCl_3$ or PBr_3 (2.5 mmol), DMF (5.0 mL), 90 °C. [b] Isolated yields. [c] A complex mixture was obtained. [d] **1 h** (1.0 mmol), PBr_3 (3.0 mmol), DMF (5.0 mL), 60 °C.

As presented above, our findings provide the first evidence that highly substituted Cps can be constructed from divinyl ketones under Vilsmeier conditions. Moreover, this method is one of the simplest due to the readily available substrates, simple procedure and cheap reagents.[1,2,8] Pleasingly, Cps **2′** and **2″** could also be prepared from divinyl ketones **1′a–c** without ketene dithioacetal functionality, respectively (Scheme 2). Whereas, the reaction of **1′d** at 90 °C only give 2-cyclopentenone **III′d** in 90% yield. The desired penta-substituted Cp could not been obtained even with prolonged reaction time at reflux (Scheme 2).[11] These results give further evidence of the VR-promoted Nazarov cyclization and the scope and limitation for the preparation of persubstituted Cps through the above mentioned sequence.

On the basis of the experimental results and related reports on Nazarov cyclizations[3,4] and reactions under Vilsmeier conditions,[6,7,12] a possible mechanism for the formation of halo-Cps **2** is proposed in Scheme 3. The reaction begins with the generation of pentadienyl cation **I** from divinyl ketones **1** induced by VR (for example, chloromethyleneiminium salt) which plays the role of an acid to initiate a 4π-electro-cyclization (**I** to **II**).[3,4] Then, the elimination of a proton from oxyallyl cation **II** leads to the enol intermediate **III** along with the release of HCl. Finally, the addition of HCl to enol **III**[12] and subsequent elimination of DMF and proton affords halo-Cps **2**. 2-Cyclopentenone **IIIa** was detected along with the formation of Cp **2a** by controlling the reaction conditions.[13] The above mechanism indicates that the Nazarov cyclization



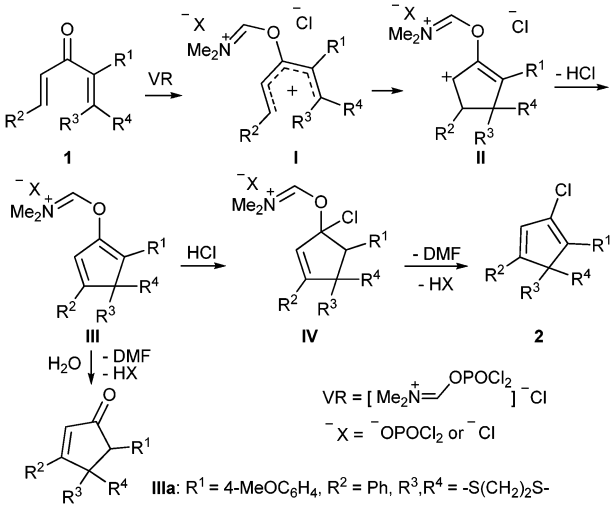
Scheme 2 Synthesis of **2′** and **2″** from **1′** under Vilsmeier conditions.

sequence is diverted (**III** to **IV**) after the elimination step (**II** to **III**) but before the reprotonation of the enol **III**.

It is noteworthy that this tandem Nazarov cyclization–halovinylation process provides various functionalized cyclopentadienes, in which either a halogen or a dithioacetal functional group are included. To explore the synthetic potential of these cyclopentadienes **2**, the [4 + 2] cycloaddition[14] of **2** with dimethyl acetylene dicarboxylate were tried and an interesting transformation leading to polyaryls **3** was found. As described in Table 2, upon treatment of the selected **2a**, **2c** or **2e** (1.0 mmol) with dimethyl 2-butynedioate (5.0 mmol) in toluene (5.0 mL) at reflux, polyaryls **3a–c** bearing the *p*-terphenyl or *p*-quaterphenyl motif[15] were produced in a regiospecific manner in high yields. It is clear that cyclopentadienes **2** act as cyclopentadienone equivalents[8] in [4 + 2] cycloaddition reactions.

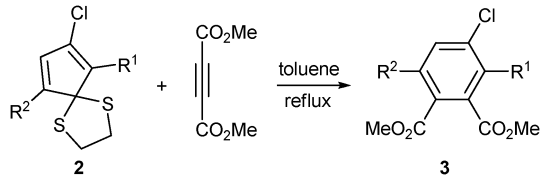
In conclusion, a novel tandem Nazarov cyclization-halovinylation strategy is developed for the synthesis of highly substituted Cps. The simplicity of execution, readily available substrates, cheap reagents, and broad range of potential products and applications[1,8] make this synthetic strategy more efficient and deserving of further attention.

We gratefully acknowledge NNSFC-20972029/20872015, NENU-STC08007/07007 for funding support of this research.



Scheme 3 Proposed mechanism for tandem Nazarov cyclization–halovinylation of **1** mediated by Vilsmeier reagent.

Table 2 Synthesis of polyaryls **3** by [4 + 2] cycloaddition of cyclopentadienes **2** with dimethyl 2-butynedioate[a]



Entry	2	3	R^1	R^2	t/h	Yield (%)[b]
1	**2a**	**3a**	4-$MeOC_6H_4$	C_6H_5	8.0	87
2	**2c**	**3b**	4-$MeOC_6H_4$	4-biphenyl	8.0	91
3	**2e**	**3c**	4-$MeOC_6H_4$	4-ClC_6H_4	9.0	90

[a] Reagents and conditions: **2** (1.0 mmol), dimethyl 2-butynedioate (5.0 mmol), toluene (5.0 mL), reflux. [b] Isolated yields.

Notes and references

‡ **General procedure for the synthesis of cyclopentadienes 2 (taking 2a as an example)**: to a well-stirred solution of **1a** (354 mg, 1.0 mmol) in DMF (5.0 mL) was added $POCl_3$ (0.23 mL, 2.5 mmol) in one portion at room temperature. Then, the reaction mixture was heated to 90 °C and stirred for 2.5 h. After **1a** was consumed (monitored by TLC), the reaction mixture was poured into water (30 mL), neutralized with saturated aqueous $NaHCO_3$ to pH 7, and extracted with CH_2Cl_2 (15 mL × 3). The combined organic extracts were washed with water (15 mL × 3), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent, petroleum ether–diethyl ether: 75/1, v/v) to give **2a** (320 mg, 86%) as light yellow crystals.

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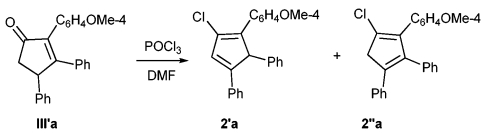
9 The intramolecular oxa/aza-Michael additions of α-alkenoyl ketene dithioacetals with R^1 = CO_2Et or CONHAr under Vilsmeier conditions were found to afford δ-lactones and δ-lactams, respectively. See: J. Liu, M. Wang, F. Han, Y. Liu and Q. Liu, *J. Org. Chem.*, 2009, **74**, 5090.

10 Crystal data for **2f**: $C_{20}H_{16}ClNO_3S_2$, yellow, M = 417.91, monoclinic, space group $P21/c$, a = 6.808(2), b = 16.045(5), c = 18.120(6) Å, V = 1967.4(11) Å^3, α = 90.00, β = 96.286(6), γ = 90.00, Z = 4, T = 273(2) K, F000 = 864, 10 854 reflections collected, 3885 unique with R(int) = 0.0338, R_1 = 0.0603, wR_2 = 0.1416 ($I > 2\sigma(I)$).

11 It was found that cyclopentenone **III′a**, independently obtained from the Nazarov cyclization of **1′a** mediated by concentrated HCl (3.0 equiv) in CH_2Cl_2 at room temperature, could afford cyclopentadienes **2′a** and **2′′a** in 39% and 40% yields, respectively, by treatment with $POCl_3$ (2.5 equiv) in DMF at ambient conditions for 1.5 h. For experimental details, see ESI.†



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13 For details, please see ESI.† As a comparison, no reaction was found when **1a** (1.0 mmol) was treated with either concentrated HCl (3.0 equiv) or dry HCl gas (bubbled into the reaction mixture) in 5.0 mL of DMF at 90 °C for 3.0 h. These results provided further support for the proposed mechanism in Scheme 3.

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