

Multistep One-Pot Wittig/Nazarov Reaction for Construction of Cyclopentenone with Diazo Compounds and Acid Chlorides

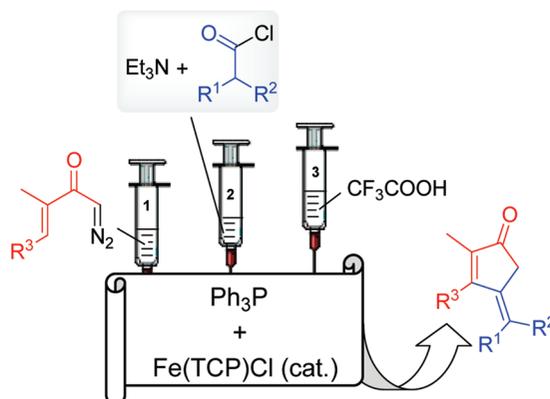
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ABSTRACT



A facile multistep one-pot synthesis of single or fused cyclopentenones has been developed. The sequence involves a transition metal-catalyzed ylide formation/Wittig Olefination/Nazarov Cyclization.

The design and implementation of new economically sustainable synthetic processes is one of the major challenges in modern organic synthesis. The application of cascade or domino¹ and tandem² reactions in a “one-pot” manner offers a straightforward method for the construction of new bonds

simultaneously or in a stepwise manner without the isolation of the intermediates, making the whole procedure economically sustainable and environmentally conscientious. Nowadays, multistep one-pot reactions have emerged as valuable tools in organic synthesis for reducing operative steps, simplifying purification procedures and enhancing synthetic efficiency,

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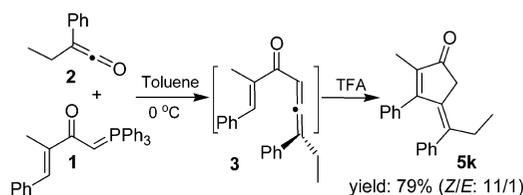
which saves solvents and resources. However, it is difficult to efficiently and chemoselectively control one-pot, multistep reactions, due to the mutual interference among various components. Herein, we report a successful example of multistep one-pot synthesis of β -methylene cyclopentenones through the Wittig/Nazarov reactions using unsaturated diazocarbonyl compounds and acyl chloride as the precursors of vinyl allenes.

As our ongoing research project on ylide chemistry,³ we recently developed a novel efficient method of allene synthesis via transition metal-catalyzed reaction of diazocarbonyl compounds with phosphines and ketenes⁴ in which a variety of di- and trisubstituted allenes can be obtained by olefination of ketenes with EDA in the presence of Ph₃P and tetra(*p*-chlorophenyl)porphyrin iron chloride (Fe(TCP)Cl). Allenes, owing to their unique chemical properties, are demonstrated as important synthetic building blocks in various reactions such as cycloadditions, cycloisomerizations, cross-coupling reactions and the Nazarov reaction.^{5–10} The first Nazarov cyclization of an allenyl ketone was reported by Tius and Nagao independently.⁶ In 1998, Hashmi extended this reaction to allenyl vinyl ketones, which delivered the products on silica gel.⁷ In addition, indol-2-yl allenyl ketones were cleanly converted to the corresponding cyclopenta[b]-indole derivatives under mild conditions.⁸ A variant type of Nazarov cyclization was reported by de Lera et al. in which divinylallene acetals underwent cyclization almost quantitatively under mild conditions (TsOH).⁹ The cationic cyclopentannulation of allenyl ethers has been widely studied by Tius and constitutes a very efficient

construction of α -methylene cyclopentenones.¹⁰ We reasoned that allenyl vinyl ketones could be synthesized from the Wittig reaction of unsaturated carbonyl ylide with ketenes and might undergo cyclization efficiently in one pot.

Initial attempts were made using unsaturated carbonyl ylide **1** and ketene **2** in toluene at 0 °C. The intermediate allenyl ketone **3**, detected by ¹H NMR, subsequently underwent cyclization under acidic conditions. Among several acids (TfOH, HCl, AcOH, FeCl₃ and silica gel) examined, TFA (40 equiv) was found to be the best giving the product in 79% yield with *Z/E* ratio of 11/1 (Scheme 1).

Scheme 1. One-Pot Reactions of Ylide **1** with Ketene **2**



Although Hashmi⁷ and Forest^{10f} have shown that silica gel can serve as an excellent catalyst for Nazarov cyclizations of allenyl vinyl ketones, it was not the optimal in the current case probably due to the interference of the in situ produced Ph₃PO. Considering the synthetic difficulty of pure unsaturated carbonyl ylide **1**, we discovered that the in situ generated **1** via Fe(TCP)Cl-catalyzed reaction of diazocarbonyl compounds **4** with Ph₃P reacted with ketene **2** as well as pure **1**. As shown in Table 1, the reactions proceeded better in ether

Table 1. Effect of Reaction Conditions on the One-Pot Wittig/Nazarov Cyclization^a

entry	solvent	equiv of TFA	<i>Z/E</i> ^b	yield ^c (%)
1	EtOH	40	11/1	81
2	CH ₃ CN	40	20/1	72
3	CH ₂ Cl ₂	40	8/1	63
4	Et ₂ O	40	13/1	93
5	THF	40	9/1	88
6	DME	40	7/1	91
7	Et ₂ O	10	5/1	78
8	Et ₂ O	20	8/1	79
9	Et ₂ O	30	11/1	84
10	Et ₂ O	80	8/1	69
11 ^d	Et ₂ O	40	12/1	95

^a Conditions: a solution of diazo compound in toluene (2 mL) was slowly added in 2 h via a syringe pump to a solution of Ph₃P (1.2 equiv) and 1.0 mol % Fe(TCP)Cl in toluene (0.5 mL), 2 h at 0 °C and then quenched with the solution of TFA. ^b Determined by 300 MHz ¹H NMR. ^c Isolated yield. ^d Ketene was prepared in situ from acid chloride and Et₃N in 2 h at room temperature. For detailed procedure, see Supporting Information.

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solvents, particularly in Et₂O (entry 4). On the other hand, the amount of TFA also had some effects on the yields and *Z/E* ratios of the cyclization. Furthermore, ketene **2** prepared in situ from 2-phenylbutanoyl chloride and Et₃N also worked extremely well in such a tandem Wittig/Nazarov cyclization to afford the product in nearly quantitative yield with a similar stereoselectivity, implying no interference of byproducts Et₃N•HCl or Ph₃PO to the reaction (entry 11). Subsequent investigation showed that the aforementioned method was applicable to various aryl alkyl ketenes. As indicated in Table 2, the nature of alkyl

Table 2. One-Pot Synthesis of β -Methylenecyclopentenones **5a–i** from **4** and Acid Chlorides^a

entry	product	R ¹	R ²	<i>Z/E</i> ^b	yield (%) ^c
1	5a	C ₆ H ₅	Me	2.5/1	90
2	5b	C ₆ H ₅	<i>n</i> -Pr	12/1	86
3	5c	C ₆ H ₅	<i>n</i> -Bu	10/1	88
4 ^d	5d	C ₆ H ₅	homoallyl	40/1	76
5	5e	<i>p</i> -MeO-C ₆ H ₄	Et	10/1	84
6	5f	<i>p</i> -Cl-C ₆ H ₄	Et	18/1	93
7 ^e	5g	<i>p</i> -Br-C ₆ H ₄	Et	9/1	65
8 ^f	5h	1-naphthyl	Et	23/1	59
9	5i	Ph	Ph	–	68
10	–	cyclohexyl	–	–	trace

^a Conditions: a solution of diazo compound in toluene (2 mL) was slowly added within 2 h via a syringe pump to a solution of Ph₃P (1.2 equiv) and 0.55 mol % of Fe(TCP)Cl in toluene (0.5 mL). Ketene was generated in situ from acid chloride and Et₃N in 2 h at room temperature, 2 h at 0 °C and then quenched with the solution of 40 equiv of TFA in 2.5 mL Et₂O. ^b Determined by 300 MHz ¹H NMR. ^c Isolated yield. ^d Ketene was generated in situ in 40 min. ^e Ketene was generated in situ in 1 h. ^f Ketene was generated in situ within 5 h at 40 °C.

substituents on ketenes had little influence on the yields (entries 1–3). Ketene with homoallyl group reacted smoothly to give alkenyl cyclopentenone in good yield (entry 4). The steric and electronic effects of substituents on aryl ring had some influence on the yields (entries 5–8). Diaryl substituted ketene also gave good yield (entry 9). Ketene derived from cyclohexanecarboxylic acid did not work (entry 10). High *Z/E* ratios of the exocyclic alkene were observed in all products, except for **5a** (entry 1).

Encouraged by the successful tandem Wittig/Nazarov reaction of **4**, a series of conjugate unsaturated diazocar-

bonyl substrates were prepared to further investigate the reaction scope. As shown in Table 3, a wide range of vinyl

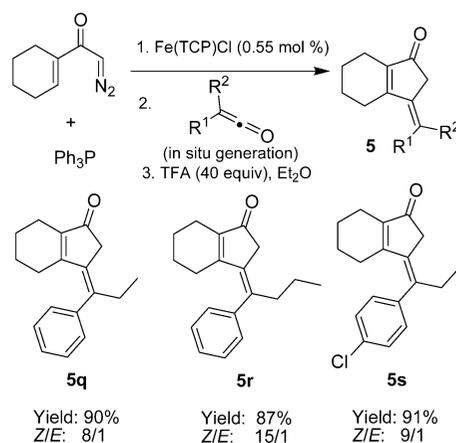
Table 3. Tandem Wittig/Nazarov Cyclization with Alkenyl Diazoketones^a

entry	products	R ³	<i>Z/E</i> ^b	yield (%) ^c
1	5j	<i>p</i> -MeOC ₆ H ₄	10/1	87
2	5k	C ₆ H ₅	12/1	95
3	5l	<i>p</i> -ClC ₆ H ₄	17/1	82
4	5m	2-furyl	15/1	80
5	5n	C ₆ H ₄ CH=CH	24/1	71
6	5o	C ₆ H ₁₁	15/1	90
7 ^d	5p	Cyclohexyl	11/1	63

^a Conditions: a solution of diazo compound in toluene (2 mL) was slowly added in 2 h via a syringe pump to a solution of Ph₃P (1.2 equiv.) and 0.55 mol % of Fe(TCP)Cl in toluene (0.5 mL). Ketene was generated in situ from acid chloride and Et₃N within 2 h at room temperature, 2 h at 0 °C and then quenched with the solution of 40 equiv of TFA in 2.5 mL Et₂O. ^b Determined by 300 MHz ¹H NMR. ^c Isolated yield. ^d 1.1 mol % of Fe(TCP)Cl, diazo compound was slowly added in 3 h via a syringe pump.

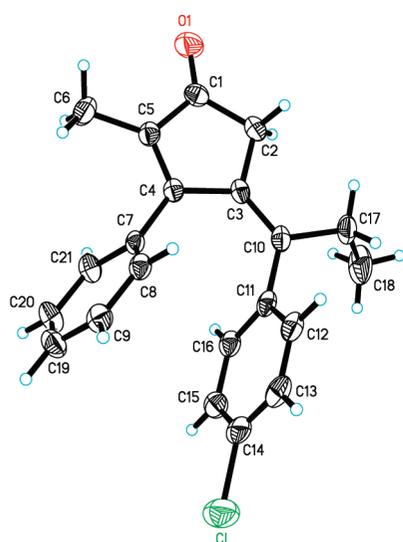
diazoketones underwent cyclization smoothly in good yields with high *Z/E* ratios. Such method can also be used to prepare fused carbocyclic rings from 1-cyclohexenyl-2-diazoethanone in excellent yields with very good stereoselectivity, which adds to the versatility of the process (Scheme 2).

Scheme 2. One-Pot Synthesis of Hexahydroindenone from 1-Cyclohexenyl-2-diazoethanone

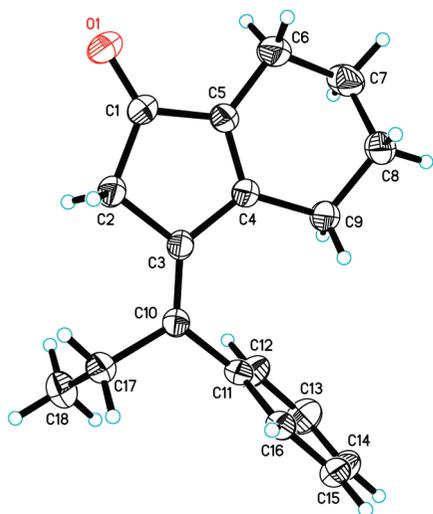


Attempts to determine the *Z/E* selectivity of the cyclization products by ¹H NMR techniques were unsuccessful due to the invisible NOE. Fortunately, the molecular structures of the major isomers of products **5f** and **5q** were established by single-crystal X-ray analyses (Figure 1), which showed that the Nazarov cyclization reactions favored *Z* selectivity.¹¹

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(Z)-5f

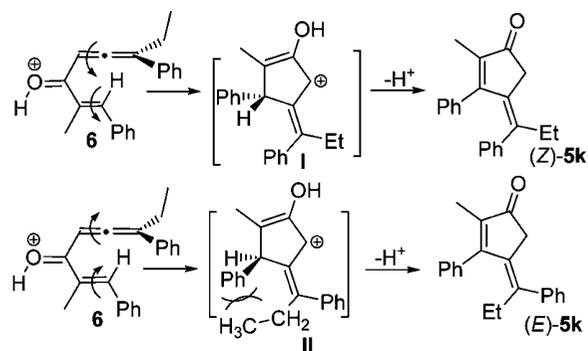


(Z)-5q

Figure 1. X-ray structures of the major isomers of **5f** and **5q**.

The high stereoselectivity can be explained very well as shown in Scheme 3. The cyclization proceeded via conro-

Scheme 3. Proposed Stereochemical Model



tation ring closure. Since the produced intermediate **I** is more stable than intermediate **II** due to the steric effect, *Z*-product were obtained as the major ones.¹²

In conclusion, we have developed a novel Wittig/Nazarov cyclization reaction, which offers a straightforward method for the construction of β -methylene cyclopentenones in a multistep one-pot manner without the isolation of intermediates. The high yield, excellent stereoselectivity, mild reaction conditions as well as simple purification procedures make this method very attractive to the synthesis of cyclopentenone derivatives.

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) CCDC 714457 (**5f**) and CCDC 714458 (**5q**) contain the supplementary crystallographic data.

(12) *E*-**5k** didn't isomerize into *Z*-**5k** under the reaction conditions.