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Pericyclic Reaction of a Zwiterionic Salt of an Enedione-diazoester. A Novel Strategy for the Synthesis of Highly Functionalized Resorcinols

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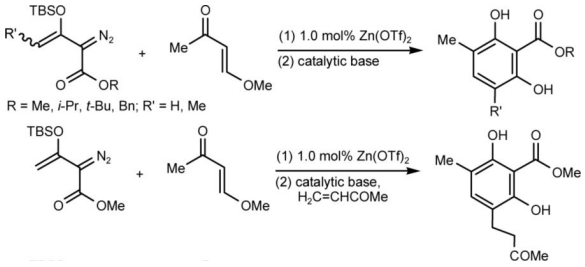
Abstract



Enedione-diazoesters formed from 3-TBSO-2-diazo-3-butenoates undergo base catalyzed pericyclization that with dinitrogen extrusion and methyl migration provide a novel and efficient route to 2-carboalkoxyresorcinols. Intercepting the intermediate enolate anion with methyl vinyl ketone leads to the corresponding 4-substituted-2-carboalkoxyresorcinol and suggests generalization of this methodology.

Resorcinol and its derivatives are important ingredients for the total synthesis of a number of natural products and phenolic compounds of pharmaceutical interest.[1,2] However, with few exceptions[3,4] general methods for their synthesis are difficult to achieve except through traditional methodologies that originate with resorcinol.[1] We wish to report a new methodology for the synthesis of 2-carboalkoxyresorcinols, based in part on serendipity, that relies on a convenient procedure that we recently reported for the synthesis of diverse α-diazo-β-keto esters.[5] This procedure uses the readily accessible 3-TBSO-substituted vinyldiazoacetate **1** for zinc triflate-catalyzed Mukaiyama-Michael reactions with α,β-unsaturated ketones resulting in functionalized 3-keto-2-diazoalkanoates in high yield and selectivity (Scheme 1). The methodology for resorcinol synthesis employs a functionalized α,β-unsaturated ketone that undergoes elimination to an enedione-diazo ester which is susceptible to an unprecedented pericyclic reaction and rearrangement.

In examining the breadth of the Mukaiyama-Michael transformation of **1** and its applications, we employed *trans*-4-methoxy-3-buten-2-one (**2**) as the substrate with the expectation that an enolizable enedione[6] would be formed whose chemistry could lead us to cycloaddition products that contained the diazoester functionality. As anticipated, the direct Mukaiyama-Michael product (**3**) was unstable, undergoing elimination under the reaction conditions to form α,β-unsaturated ketone **4** exclusively (Scheme 2),[7] but the resulting enedione underwent an

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Supporting Information Available. General experimental procedures, structure of **13b**, and spectroscopic data for all new compounds. This material is available free of charge via the internet at http://pubs.org.edu.

unexpected transformation resulting in the formation of a substituted resorcinol. Examination of this process showed a diverse chemistry that we now report.

Attempted chromatographic purification of **4** on silica gel resulted in the loss of **4**, but the highly substituted resorcinol **5** was isolated in low yield (13%) (Scheme 3). Various conditions were employed to optimize formation of this unexpected reaction product by first treating **1** and **2** with zinc triflate and then, after concentrating the mixture but without isolating **4**, adding a suitable promoter to catalyze the formation of the resorcinol product. Since compound **4** decomposes upon contact with silica gel, silica gel was added to the reaction system; however, only migration of the enone double bond occurred (36% conversion to **6**). Performing the reaction at elevated temperature with silica gel or by adding acetic acid to the system produced the same results. When 2.0 molar equiv of 4 *N* aqueous HCl was used, **5** was produced in 21% isolated yield. However, assuming that enolization of **4** is one of the key steps for this transformation, we anticipated that the addition of base would facilitate this reaction. With 5.0 equivalents of triethylamine, **5** was obtained in 45% isolated yield, but the yield of **5** was further improved when only a catalytic amount of aqueous sodium hydroxide (0.10 mol/L NaOH, 10 mol %) was employed; and under these catalytic conditions **5** was isolated in 83% yield.

A plausible mechanistic pathway for resorcinol formation is presented in Scheme 4. Removal of the most acidic proton from compound **4** produces the conjugated enolate anions that are depicted by intermediates **7**. Isomerization of **7a** in which the 5,6-positions have the E-geometry to **7b** in which the 5,6-positions have the Z-geometry is critical to the second isomerization in which the two ends are wrapped together (**7c**) through a conjugated triene that is appropriately arranged for pericyclization. Similar 6-π electrocyclizations involving enolate derivatives have been reported,[8] although none have involved a diazo compound.

The diazonium ion intermediate **8** resulting from pericyclization is suitably positioned to undergo loss of dinitrogen in concert with methyl migration to form intermediate **9** that is the tautomer of the observed resorcinol product. The conversion of **8** to **9** is, to our knowledge, unprecedented; also, instead of undergoing methyl migration to the carbon bearing the diazonium ion that would be a semi-pinacol rearrangement[9] or, alternatively, forming an epoxide[10] with loss of dinitrogen, the methyl group migrates in the reverse direction to that of dinitrogen extrusion. The formation of the phenolate anion that can continue proton removal from reactant **4** is consistent with the need for only a substoichiometric amount of base to complete the reaction; after the reaction is initiated, the transformation is self sustained.

Ester derivatives of **4** were prepared and subjected to the same conditions as those used for the synthesis of **5**. The coresponding resorcinol products were formed (Table 1), but their isolated yields were only moderate, and an additional product (**13**) accompanied the derivative resorcinol (eq 1). This compound, which was not observed from reactions with **4**, resisted interpretation until an x-ray crystal structure of compound **13b** revealed the 1,2-diazepine structure (Figure 1).

The formation of **13** can be understood as arising from an 8π-electrocyclization for which we are aware of few previous examples.[11] The origin of the 1,2-diazepine precursors in prior studies has been cyclobutene-substituted diazoacetates or TMS-diazomethyl compounds that undergo electrocyclic ring opening to the requisite cisdienyldiazo intermediate that is structurally situated to undergo 8π-electrocyclization. The production of **13**, and its absence in the reactions of **4** that produce **5**, may be due to steric resistance to the coiling of **7a** to **7c** that preceeds electrocyclization in the formation of resorcinol derivatives (Scheme 4) and, indeed, the yield of **13** varies with the steric bulk of the ester. Accordingly, the pathway to **13** can be understood as arising from deprotonation of **4** to form enolate **7a** that isomerizes to **7d** before undergoing electrocyclization (Scheme 5).

In an effort to examine the generality of this novel cyclization process, substituted vinyl ketone **15** was employed, and the resultant resorcinol **16** was formed in moderate yield (Scheme 6). Reactant **15** was prepared from methyl 2-diazo-3-ketopenanoate. Compound **17** has been used as an atraric acid derivative for treatment of benign prostate hyperplasia, prostate carcinoma and spinobulbar muscular atrophy.[12]

The pathway to substituted resorcinols that is described in Scheme 4 involves initial formation of enolate **7** that was expected to be suitable for trapping by Michael acceptors.[13] If isomerization from the original E-isomer to the Z-isomer (**7a** to **7b** in Scheme 4) is the limiting factor, then reaction of **7** with a Michael acceptor should not only be possible, yielding product with the same E olefin geometry, but also make possible further reaction that results in additional functionalization of the resorcinol core. Accordingly, treatment of **4** with a catalytic amount of sodium hydroxide in the presence of 4.0 molar equiv. of methyl vinyl ketone at 0° C resulted in the formation of Michael addition product **18** in 65% isolated yield (Scheme 7); **18** was the sole addition product, and resorcinol **19** was not formed under these conditions. The Michael addition product **18** was sufficiently robust to survive silica gel purification, which was not the case for **4**. Subsequent treatment of **18** with triethylamine at room temperature resulted in the formation of resorcinol **19** in 45% isolated yield, thus further demonstrating the versatility of the methodology.

In summary, enedione-diazoesters undergo a novel base-catalyzed pericyclization that, with subsequent dinitrogen extrusion and alkyl migration, forms 2-carboalkoxyresorcinols in good yield. Interception of the enolate intermediate on the pathway to pericyclization by a Michael acceptor, and its subsequent conversion to a 4-substituted-2-carboalkoxyresorcinol, suggests the synthetic potential of this methodology. Efforts are underway to further develop this novel synthetic process.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(7). Compound **3** was produced when the zinc triflate catalyzed reaction was performes in the presence of molecular sieves 4A; A mixture of *cis* and *trans* isomer in about 2/1 ratio was observed by NMR.

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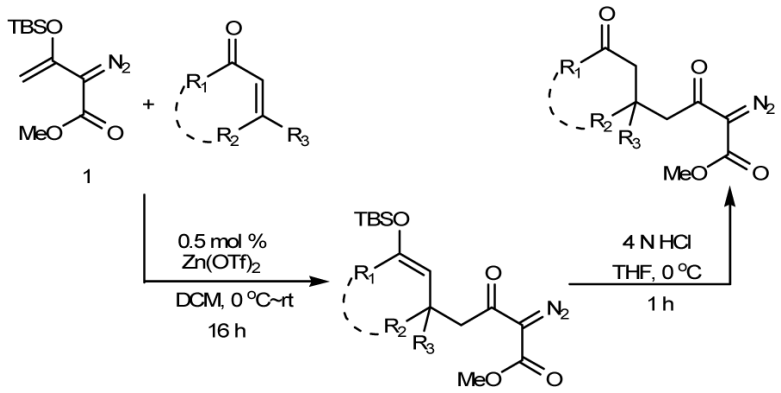
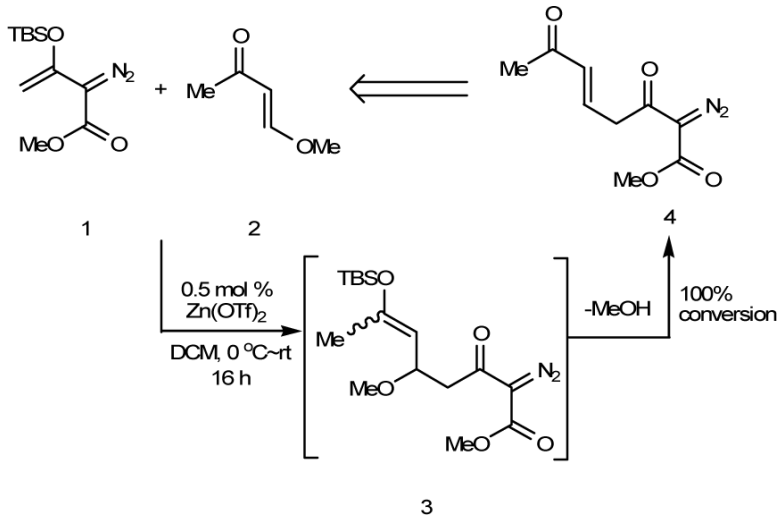
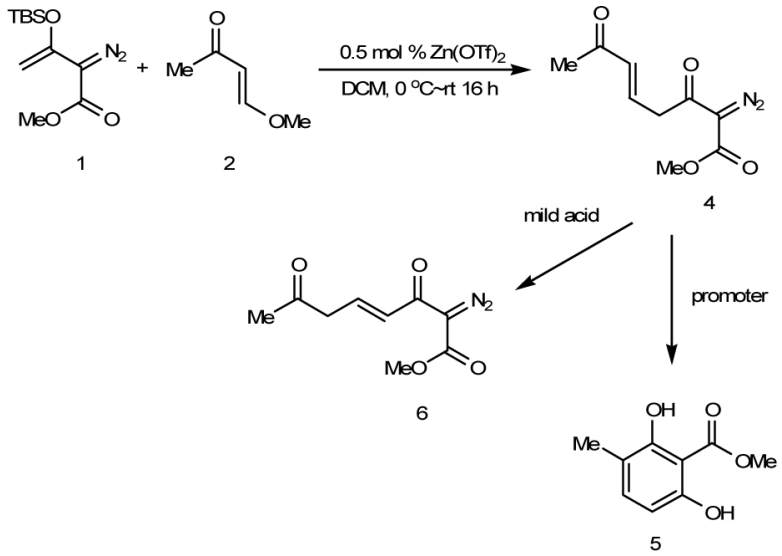


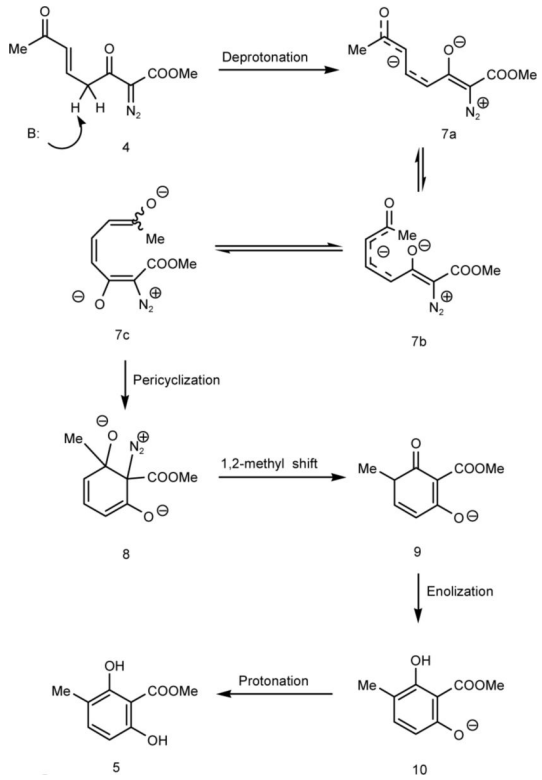
Scheme 1.
Mukaiyama-Michael Reactions of TBSO-Substituted Vinyldiazoacetate **1**



Scheme 2.
Mukaiyama-Michael Reaction with 4-Methoxy-3(*E*)-buten-2-one



Scheme 3.
Reactions of Methyl 2-Diazo-3,7-dioxo-5(*E*)-octenoate



Scheme 4.
Base-catalyzed Pericyclization-rearrangement of **4**

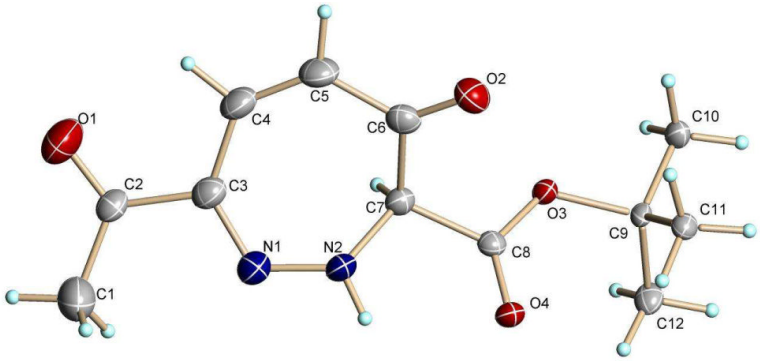
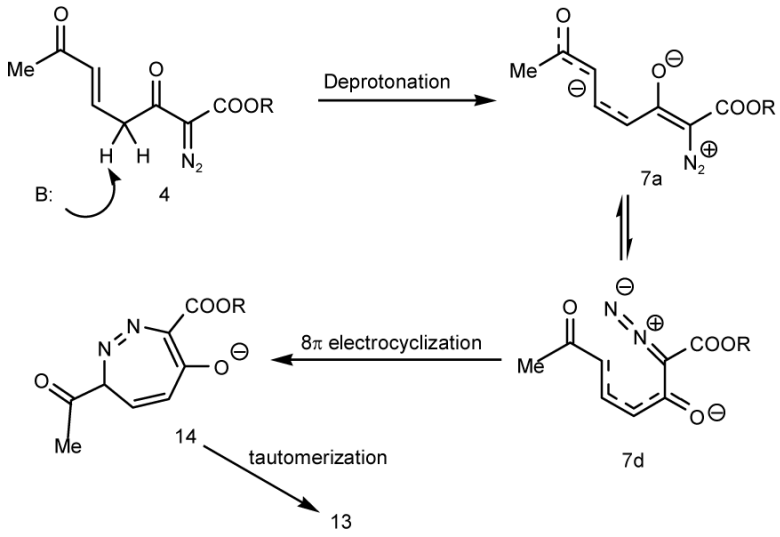
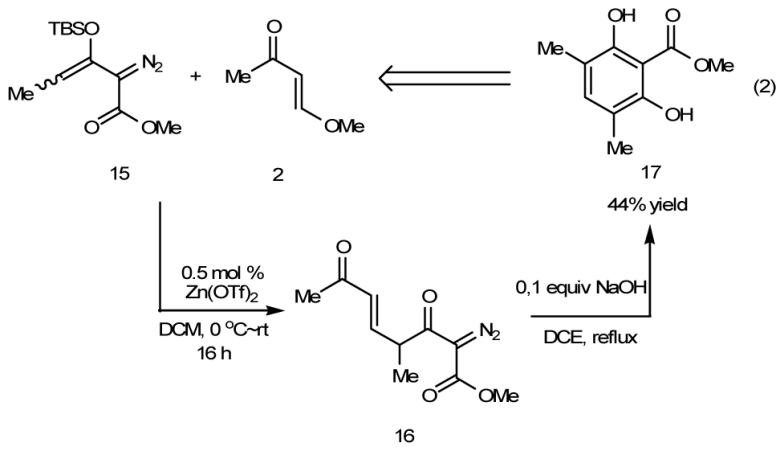


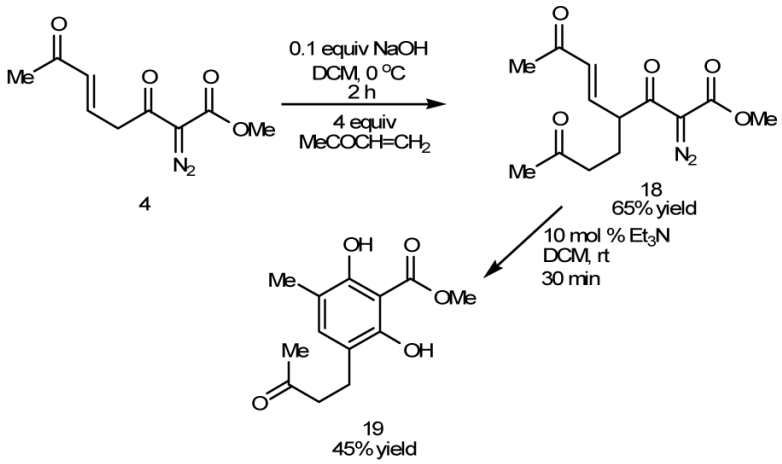
Figure 1.
X-ray structure of 1,2-Diazepine **13b**.



Scheme 5.
Pathway to 1,2-Diazepines **13**



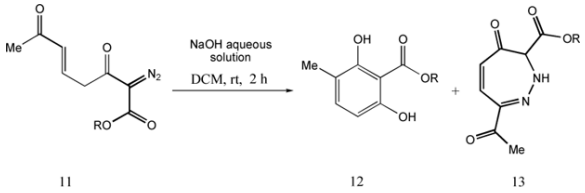
Scheme 6.
Synthesis of Atraric Acid Derivative



Scheme 7.
Michael Addition/Pericyclization/Rearrangement

Table 1

Influence of Alkyl Ester on Resorcinol Formation from Alkyl 2-Diazo-3,7-dioxo-5(*E*)-octenoate.



11 12 13

(1)

	R	equivalents of NaOH	yield[a] 12+13 (%)	ratio[b] (12:13)
a	*i*-Pr	0.1 equiv	73	81:19
	i-Pr	0.2 equiv	67	79:21
b	*t*-Bu	0.1 equiv	68	79:22
	t-Bu	0.2 equiv	72	73:27
c	Bn	0.1 equiv	66	71:29
	Bn	0.2 equiv	73	67:33

[a] Yield of isolated products after column chromatography.

[b] Ratio based on isolated yields of compounds 5 and 14.