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Org Lett. Author manuscript; available in PMC 2011 October 1.

Published in final edited form as:
Org Lett. 2010 October 1; 12(19): 4304–4307. doi:10.1021/ol101744h.

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

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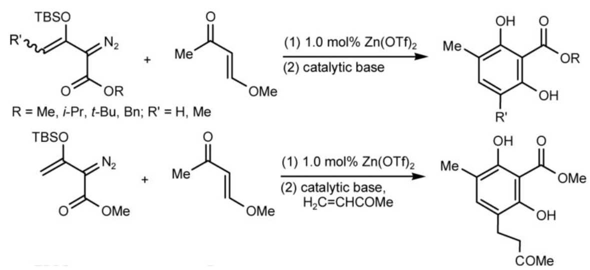
Abstract



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.

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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).

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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

We are grateful to the National Institutes of Health for their financial support of this research (GM46503). We wish to thank Arnold R. Romero Bohórquez of the Laboratorio de Química Orgánica y Biomolecular, Escuela de Química, Universidad Industrial de Santander in Bucaramanga, Colombia for early efforts in this research.

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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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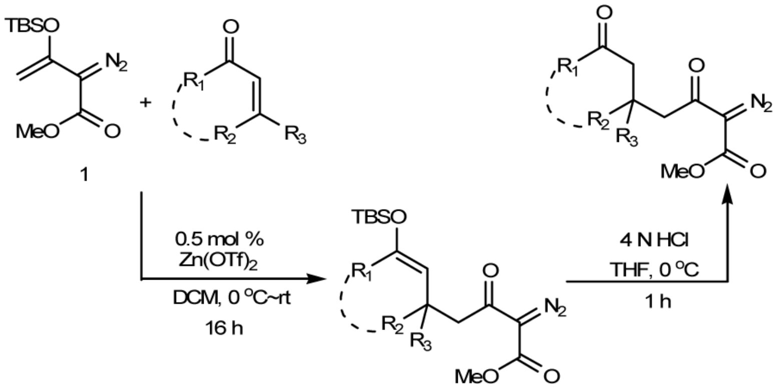

Scheme 1.
Mukaiyama-Michael Reactions of TBSO-Substituted Vinyldiazoacetate **1**

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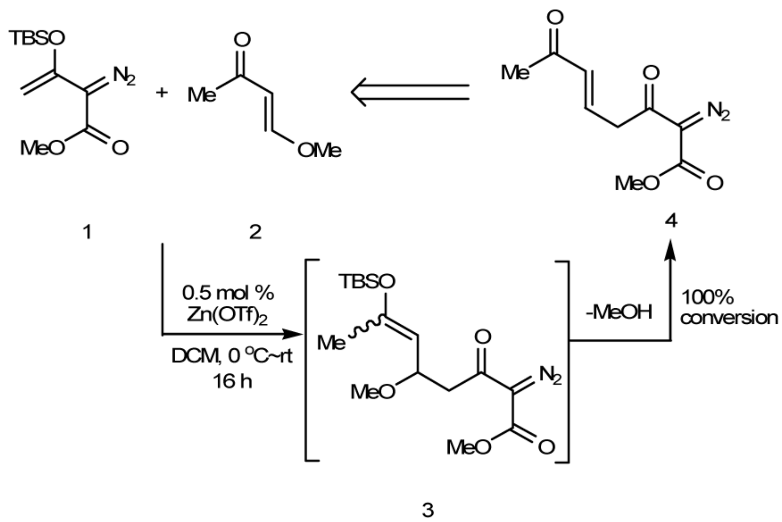

Scheme 2.
Mukaiyama-Michael Reaction with 4-Methoxy-3(*E*)-buten-2-one

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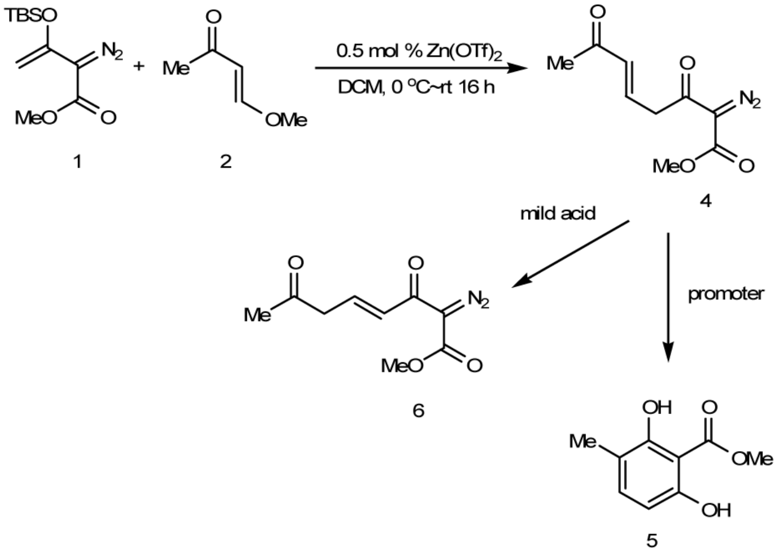
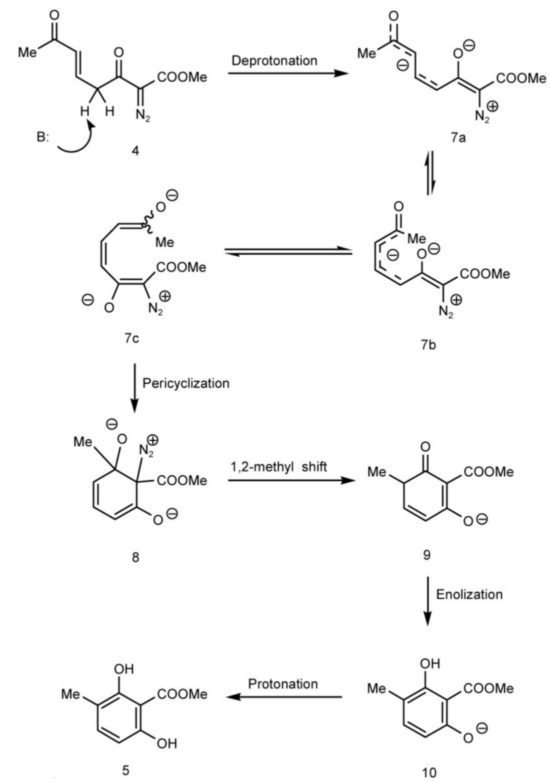


Scheme 3.

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



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

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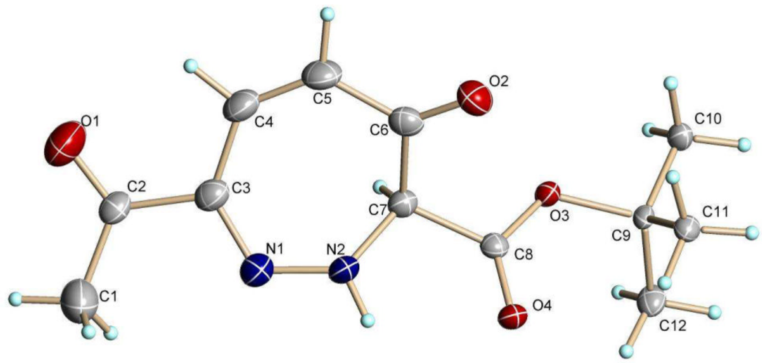
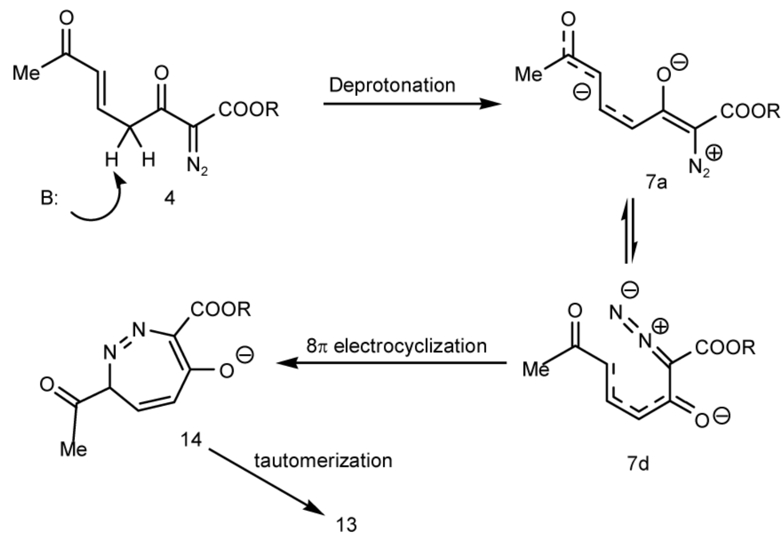


Figure 1.
X-ray structure of 1,2-Diazepine **13b**.



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

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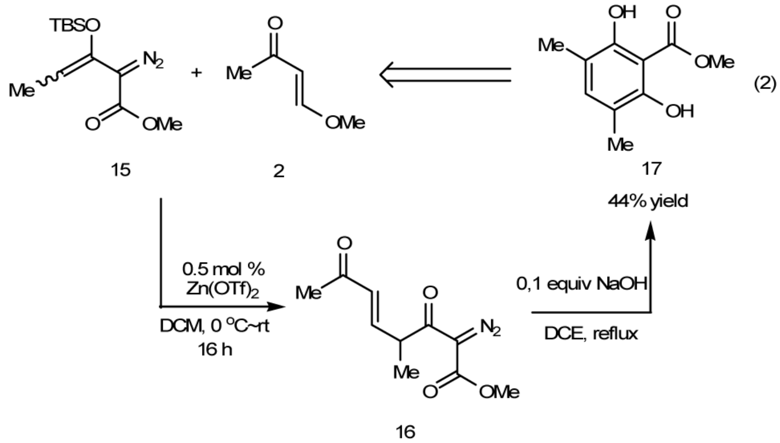
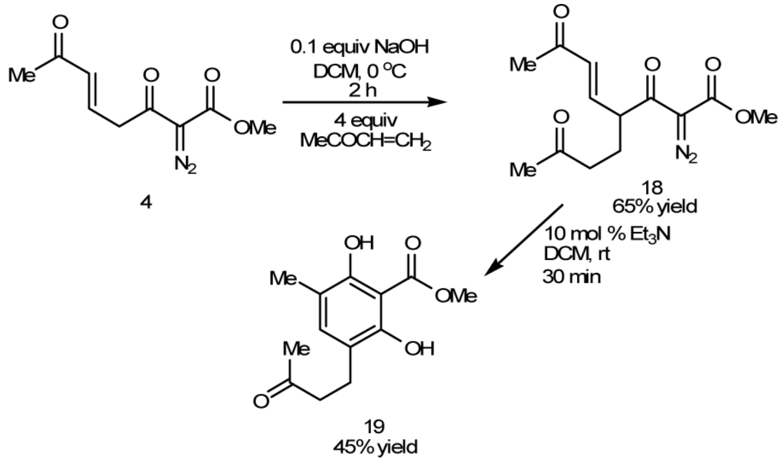


Scheme 6.
Synthesis of Atraric Acid Derivative



Scheme 7.
Michael Addition/Pericyclization/Rearrangement

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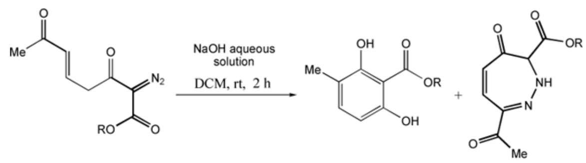
Table 1

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.