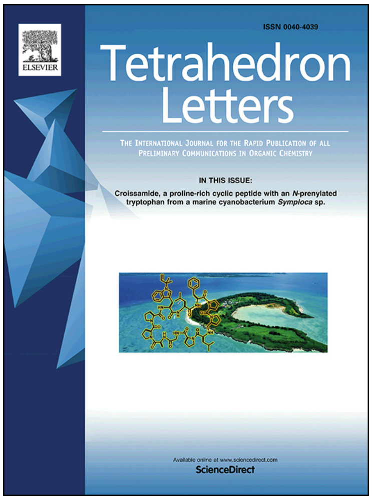

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Graphical Abstract

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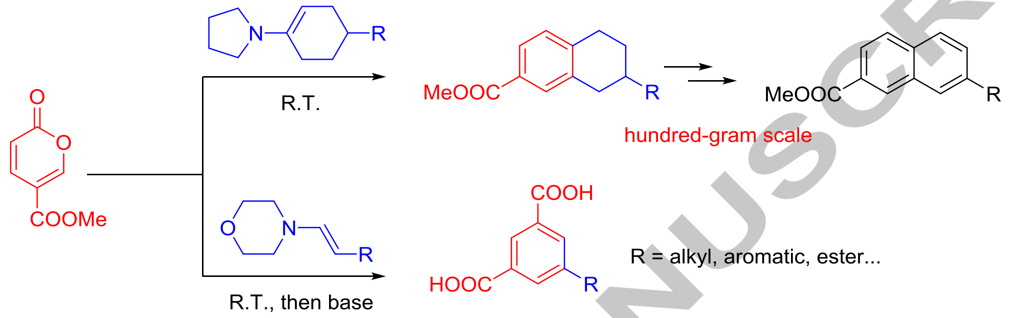

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Divergent Pathways to Isophthalates and Naphthalate Esters From Methyl Coumalate

Huangchao Yu[a] , George A. Kraus [a,]*

[a] *Department of Chemistry, Iowa State University, Ames, IA 50010,U.S.A.*

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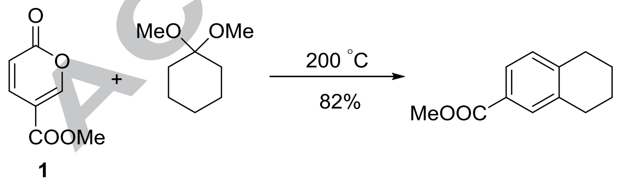
ABSTRACT

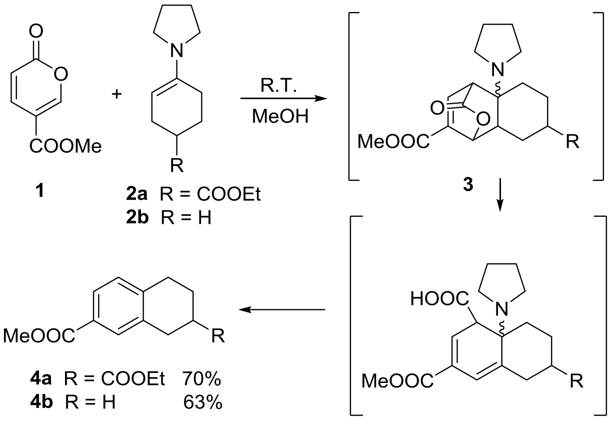
Methyl coumalate readily reacts with enamines at ambient temperature to give lactones, which can be further transformed into isophthalates and tetrahydronaphthoates. Both cyclic and acyclic enamines show good reactivity. Dehydrogenation of tetrahydronaphthoate 4a was achieved on a hundred-gram scale.

A number of pyrones have been employed in cycloaddition reactions.[1] The most common cycloaddition reaction of pyrones is the Diels-Alder reaction. This area has been reviewed by Posner.[2] Van Saun has reported that the reaction between pyrone and enamines provided benzoates at elevated temperature.[3] Kraus and co-workers have shown that ketals reacted with methyl coumalate (**1**) to provide excellent yields of aromatic esters.[4] This reaction, shown in Scheme 1, occurred through a vinyl ether intermediate and is an example of an inverse electron demand Diels-Alder reaction. The reaction of methyl coumalate with a pre-formed vinyl ether is also known[5] and generates bicyclic lactone intermediates which can be converted into natural products[6,7,8] and into isophthalates.[9]



Scheme 1. Methyl coumalate reacts with ketal.

Although the ketal required 200 °C for a successful reaction, we report herein that the use of the pyrrolidine enamine shown in Scheme 2 allows the cyclization/elimination to the tetrahydronaphthoate to proceed at ambient temperature without isolation of the lactone. We believe that the unfavorable nonbonded interactions in the tricyclic lactone **3** led to a bicyclic amino acid that readily extruded carbon dioxide and pyrrolidine to produce **4a**. An alternative pathway that the lactone **3** released CO_2 through a retro Diels-Alder process, and then the elimination of pyrrolidine to give **4a** is also possible. This reaction was successful with the enamines of cyclohexanone and ethyl 4-oxocyclohexane-1-carboxylate.



Scheme 2. Tetrahydronaphthoate synthesis via a tandem Diels-Alder/elimination.

Interestingly, the reaction of methyl coumalate with the enamine of cyclopentanone in DCM afforded products in 23% yield as 3:1 mixture of diastereomers that lacked aromatic ring protons in the proton NMR. The major diastereomer showed the M/Z^+ at 195, the carbon resonances at 207.1 ppm and 166.8 ppm, and the three proton resonances at 7.08 ppm (1H, singlet), 7.03 ppm (1H, quartet), and 1.83 ppm (3H, doublet) support the structure shown in Scheme 3. This reaction presumably occurs via the Michael addition adduct **5**, which fragments to form an iminium intermediate **6** which is converted into **7**. The E conformation of the major product was confirmed by the NOE

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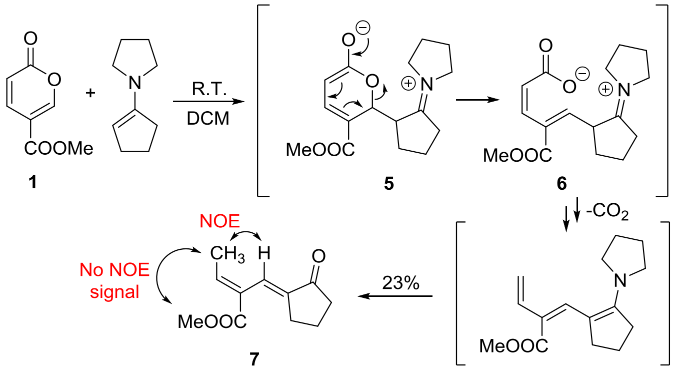
* Corresponding author. Tel.: +1-515-294-7794; e-mail: gakraus@iastate.edu

experiment, where no signal was observed between the terminal methyl group and the methyl ester.

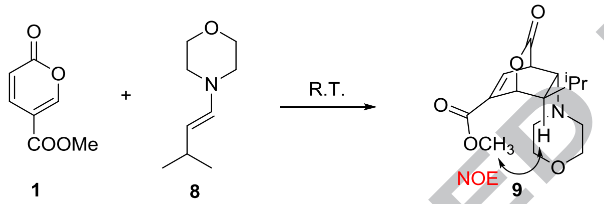


Scheme 3. Mechanism for formation of **7**.

In contrast, the reaction between the morpholine enamine of 3-methylbutanal and methyl coumalate in dichloromethane generated the stable bicyclic lactone **9** as a mixture of diastereomers (8:1 ratio) in 98% yield (entry 3). The NOE experiment indicated that the isopropyl group is in equatorial position of the major product.

The proton NMR spectrum confirmed the trans-relationship of the amine and the isopropyl group. The yield of this cycloaddition was solvent dependent with lower yields in toluene (87%), methanol (60%) and dioxane (63%), as shown in Table 1.

Table 1. D-A reaction of methyl coumalate and enamine **8**

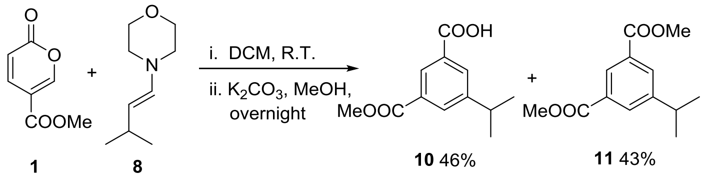


Entry	Solvent	Time (mins)	Yield (%)^a
1	Toluene	90	87
2	DCM	90	94
3	DCM	120	98^b
4	THF	90	75
5	Diethyl ether	90	74
6	DMF	90	86
7	**Methanol**	**90**	**60**
8	1,4-dioxane	90	63

^{a} Yields were calculated based on ^{1}H NMR

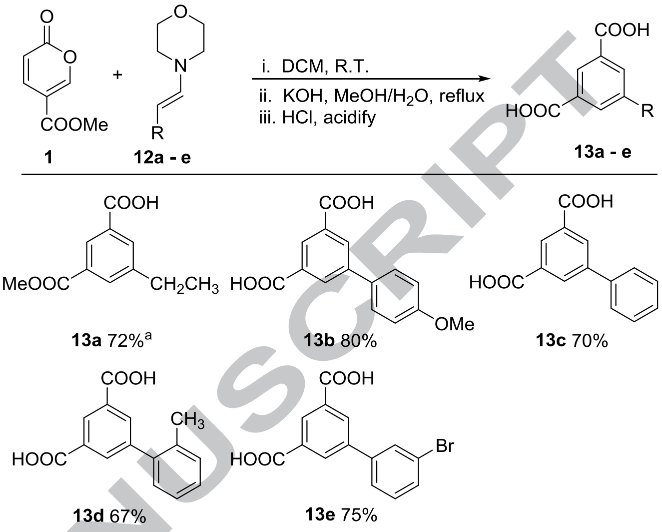
^{b} Isolated yield

Lactone **9** could readily be converted into the isophthalates **10** and **11** in 89% combined yield using potassium carbonate in methanol at ambient temperature (Scheme 4).



Scheme 4. Synthesis of isophthalate

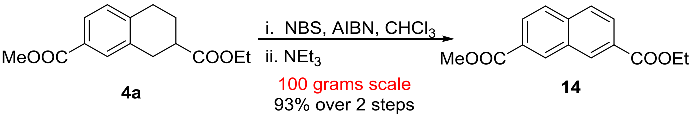
Extension of this transformation to other aldehyde enamines afforded the products depicted below in Scheme 5. Phenyl substituted isophthalates were obtained in good yields by hydrolysis in basic methanol/water solution in one pot. Enamine **12b, 12d and 12e**, with substituents at ortho, meta and para position on the aromatic ring afforded corresponding products in good yields. The enamine of isobutyraldehyde did not react with **1**.



^{a} Used K_2CO_3 as the base

Scheme 5. Synthesis isophthalic acids

The tetrahydronaphthoate **4a** was produced on a hundred-gram scale, and was readily converted into naphthalene diester **14** in 80% yield over two steps as depicted in Scheme 6. Diester **14** is a monomer for the production of polyethylene naphthalates, a class of polymers with mechanical properties superior to those of polyethylene terephthalate (PET).[10]



Scheme 6. Dehydrogenation of diester **4a**

In conclusion, the reaction of methyl coumalate with enamines provides convenient routes to substituted isophthalic acids or naphthoates depending on the structure of the enamine.

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Highlights

1. First report of the reaction between methyl coumalate and enamines
2. Direct synthesis of isophthalic acids and naphthalic diesters in good yields
3. Diels-Alder reaction proceeded at ambient temperature
4. Two-step, chromatography-free process