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Electron-Deficient Dienes. 5. An Inverse-Electron-Demand Diels–Alder Approach to 2-Substituted 4-Methoxyxanthones and 3,4-Dimethoxyxanthones

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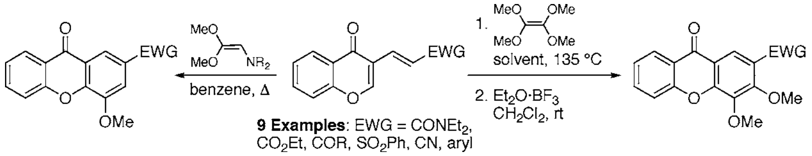
ABSTRACT



Several 4-methoxyxanthones and 3,4-dimethoxyxanthones were synthesized in good yield via inverse-electron-demand Diels–Alder (IEDDA) driven domino reactions between a series of electron-deficient chromone-fused dienes with 1-(2,2-dimethoxyvinyl)pyrrolidine or tetramethoxyethene, respectively.

More than 500 naturally occurring xanthones[1] have been isolated from higher plants, fungi, and lichens. Many of these compounds exhibit potentially useful pharmaceutical properties, e.g., antibacterial, anticancer, and inflammatory behavior.[2] Consequently, despite their relatively simple structures, xanthones continue to attract synthetic interest. A variety of general approaches to the synthesis of xanthones have been developed.[3] Classical methods involve cyclizations of benzophenones or diaryl ethers, but reaction conditions can often be harsh and the precursors can require lengthy synthesis. More recently published approaches to xanthones include 1,2-additions of organolithium reagents to dithiane-protected γ-benzopyrone-fused cyclobutenediones,[4] the condensation of benzopyranonaphthalide with Michael acceptors[5] and reactions between benzynes and 2-hydroxybenzoates.[6] Both normal and inverse-electron-demand Diels−Alder (IEDDA) reactions of 2-vinylchromone derivatives have also been applied to xanthone synthesis, but these have suffered from low to moderate yields.[7]

We reported previously that the IEDDA reaction between electron-deficient dienes **1** and electron-rich dienophiles, e.g., enamines **2**, gave 2-hydroxybenzophenones **4** instead of the desired xanthones **7** (Scheme 1).[8] The formation of **4** was explained by an elimination reaction of intermediate **3**,[9]

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(1) For a recent review, see: Vieira, L. M. M., Kijjoa, A. *Curr. Med. Chem.* **2005**, *12*, 2413.

(2) For a recent review, see: Pinto, M. M. M., Sousa, M. E., Nascimento, M. S. J. *Curr. Med. Chem.* **2005**, *12*, 2517.

(3) For a recent review, see: Sousa, M. E.; Pinto, M. M. M. *Curr. Med. Chem.* **2005**, *12*, 2447.

(4) Sun, L.; Liebeskind, L. *J. Am. Chem. Soc.* **1996**, *118*, 12473.

(5) Hauser, K. M.; Dorsch, W. A. *Org. Lett.* **2003**, *5*, 3753.

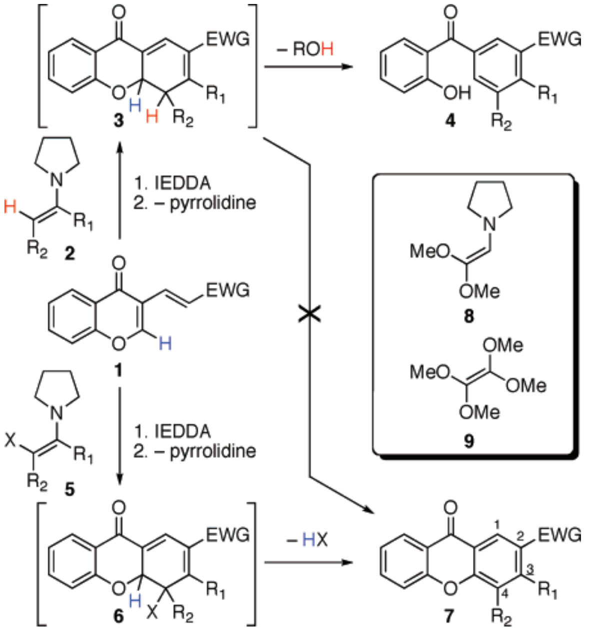
(6) (a) Zhao, J.; Larock, R. C. *Org. Lett.* **2007**, *72*, 583. This group has also recently reported xanthone synthesis via an aryl to imidazoyl migration process involving C−H activation. See (b) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2007**, *129*, 5288.

(7) (a) Ghosh, C. K.; Bhattacharyya, S.; Patra, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, *15*, 2167. (b) Kelkar, A. S.; Letcher, R. M.; Cheung, K. K.; Chiu, K. F.; Brown, G. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3732.

(8) IEDDA reactions of isomeric coumarin-fused electron deficient dienes with enamines **2** afforded benzocoumarins via a domino IEDDA / elimination / dehydrogenation sequence. See: Bodwell, G. J.; Pi, Z.; Pottie, I. R. *Synlett* **1999**, 477.

10.1021/ol702614b CCC: $40.75

Scheme 1



which was formed upon elimination of pyrrolidine from the initial IEDDA adduct.[10]

To block the pathway leading to **4** and thus be able to use dienes **1** for xanthone synthesis, two criteria were identified: the carbon atom of the dienophile that reacts with the more electron-deficient terminus of the diene should (1) bear no hydrogen atom and (2) bear a leaving group. As such, intramolecular 1,2-elimination (**3** → **4**) cannot occur. Instead, elimination of HX from **6** should furnish xanthones **7**. Dienophiles such as enamine **8** and tetramethoxyethene (TME, **9**)[11] meet these criteria and we report their use for the synthesis of several 2-substituted 4-methoxyxanthones and 3,4-dimethoxyxanthones.

Dienes **1a**–**i** were synthesized in moderate to excellent yield in one step from 3-formylchromone (**10**) using either a Wittig (**1d**),[12] a Horner–Wadsworth–Emmons (HWE)[10,12,13] (**1a**–**c**,**e**) or a decarboxylative condensation reaction[14] with the corresponding phenylacetic acid (**1f**–**i**) (Scheme 2 and Supporting Information). Noncommercially available HWE phosphonates were synthesized according to published procedures.[15]

Reaction of dienes **1a**–**i** with freshly generated enamine **8** (from dimethoxyacetaldehyde and pyrrolidine) in benzene at reflux afforded the expected xanthones **14a**–**i** in moderate to excellent yield (Table 1). Tlc analysis of these reactions showed spot-to-spot conversion of the starting materials into the products. The yields and reaction rates show a rough trend toward increasing with the strength of the electron-withdrawing group and decreasing with its steric demands. Among dienes **1a**–**f** (Table 1, entries 1–6), diene **1f**, which has a small and strongly electron-withdrawing substituent (EWG = CN), is among the fastest to react and gives one of the best yields (**14g**, 84%). The slowest of this group to react are dienes **1a** and **1e**, which have either a moderately electron-withdrawing substituent (EWG = $CONEt_2$) or a strongly withdrawing but bulky substituent (EWG = SO_2Ph). The sensitivity of both the rate and yield of the reaction to electronic effects can be seen in the behavior of the aryl-substituted dienes **1g**–**i** (Table 1, entries 7–9). All of these observations are consistent with a rate-limiting, asynchronous IEDDA reaction,[16] followed by two fast

Scheme 2

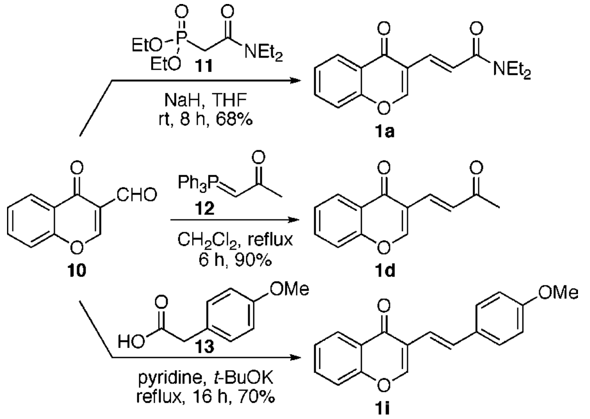
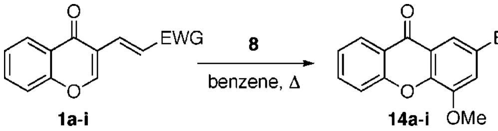


Table 1. Reactions of Dienes **1a**–**i** with Dienophile **8**



entry	EWG	product	time (h)	yield (%)
1	$CONEt_2$	**14a**	16	50
2	CO_2Et	**14b**	2	71
3	COPh	**14c**	6.5	85
4	COMe	**14d**	6	90
5	SO_2Ph	**14e**	16	70
6	CN	**14f**	2	84
7	p-$C_6H_4NO_2$	**14g**	2	70
8	C_6H_5	**14h**	17	51
9	p-C_6H_4OMe	**14i**	44	39

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(9) Mechanistically, this is an elimination reaction. Like all elimination reactions, it is an intramolecular reaction, but it differs from most others in that the reverse reaction is an intramolecular addition.

(10) Bodwell, G. J.; Hawco, K. M.; da Silva, R. P. *Synlett* **2003**, 179.

(11) Bellus, D.; Fischer, H.; Greuter, H.; Martin, P. *Helv. Chim. Acta* **1978**, *61*, 1784.

(12) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. For the preparation of the ylide leading to **1d**, see: Bell, T. W; Sondheimer, F. *J. Org. Chem.* **1981**, *46*, 217.

(13) Wadsworth, W. S. *Org. React. (N.Y.)* **1977**, *25*, 73.

(14) (a) Nohara, A.; Umetani, T.; Sanno, Y. *Jpn. Kokai Tokyo Koho* **1975**, JP50052067. (b) Silva, V. L. M. Silva, A. M. S. Pinto, D. C. G. A. Cavaleiro, J. A. S. Patonay, T. *Synlett* **2004**, 2717.

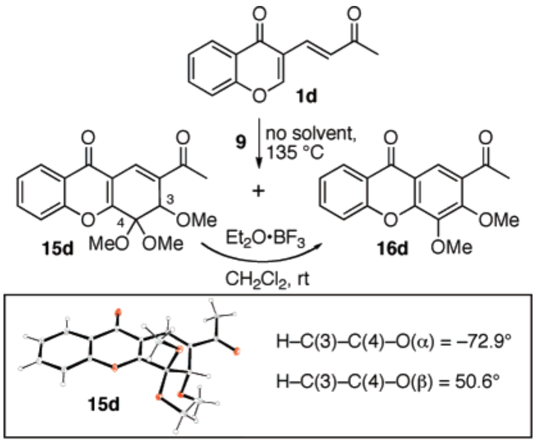
(15) For **11**, see: Watanabe, M.; Hisamatsu, S.; Hotokezaka, H.; Furukawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2810. For the phosphonate leading to **1c**, see: Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649. For the phosphonate leading to **1e**, see: Enders, D.; von Berg, S.; Jandeleit, B. *Org. Synth.* **2002**, *78*, 169.

eliminations (pyrrolidine and methanol, in either order) to give the observed 4-methoxyxanthones **14**.

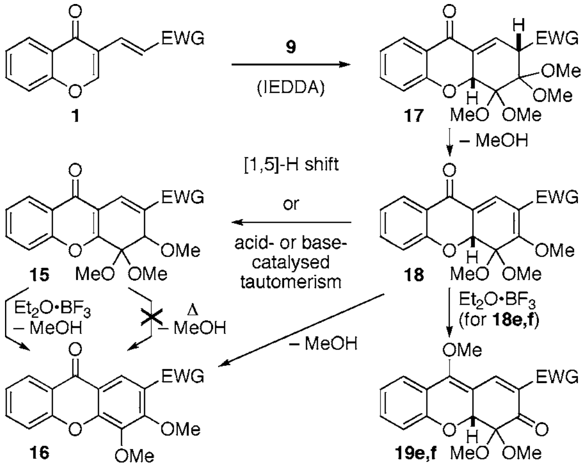
Attention was then turned to the use of tetramethoxyethene (TME) (**9**),[11] which was expected to afford 3,4-dimethoxyxanthones via an IEDDA/elimination (MeOH)/elimination (MeOH) sequence. As anticipated for this less polar and more highly substituted dienophile, it proved to be a more reluctant reaction partner. Under conditions similar to those used for the reactions of dienophile **8** with dienes **1a-i**, no reaction was observed between diene **1d** (ca. 0.2 M in benzene, reflux) and TME (5.0 equiv). The same result was obtained when toluene and then xylenes were used as the solvent.

However, when **1d** was reacted with TME at 135 °C (bp of TME = 140 °C)[11] with no solvent, the diene was consumed and xanthone **16d** (6%) was isolated as well as an unaromatized product (Scheme 3), the spectroscopic data of which were consistent with one of the expected reaction intermediates, **18d** (Scheme 4). However, its identity as an isomer, **15d** (56%), was established by crystallographic methods (see the Supporting Information). Prolonged heating of the reaction mixture at 135 °C or resubjection of **15d** to the original reaction conditions resulted in the slow formation of intractable material, but in a TLC experiment, the addition of $Et_2O{\cdot}BF_3$ to a pure sample of **15d** in dichloromethane at room temperature induced a rapid, spot-to-spot conversion to **16d**.

Scheme 3

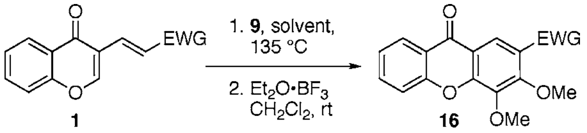


Scheme 4



Subsequent reactions of dienes **1** with TME (**9**) were heated at 135 °C, cooled to room temperature after consumption of the diene or apparent reaction cessation (TLC analysis), diluted with dichloromethane, and treated with $Et_2O{\cdot}BF_3$ (4.0 equiv) to give 3,4-dimethoxyxanthones **16** (Table 2). Good yields were obtained for **16c** (84%) and **16d** (62%), while those for **16a**,**b** and **16e**−**g** were modest (25−36%). The least electron-deficient dienes **1h** and **1i** were unreactive, giving at best only traces of product. As an exception, **1f** gave a better yield of the product (**16f**, 53%) without treatment with $Et_2O{\cdot}BF_3$.

Table 2. Reactions of Dienes **1a**−**i** with Dienophile **9**



			time (h), yield (%)			
entry	EWG	product	no solvent	xylenes	$C_2H_2Cl_4$	DMF
1	$CONEt_2$	**16a**	96, 28	192, 32	192, 40	192, 12
2	CO_2Et	**16b**	24, 36	144, 48	48, 70	
3	COPh	**16c**	24, 84		26, 90	
4	COMe	**16d**	10, 62		6, 98	
5	SO_2Ph	**16e**	2, 29	24, 21	4, 18	
6	CN	**16f**	2, 27[a]		24, 38	
7	*p*-$C_6H_4NO_2$	**16g**	23, 25[b]		48, trace[e]	
8	C_6H_5	**16h**	48, trace[c]		240, 6	
9	*p*-C_6H_4OMe	**16i**	96, 0[d]		240, 0	

[a] 53% without $Et_2O{\cdot}BF_3$ treatment. [b] 20% recovery of **1g**. [c] 60% recovery of **1h**. [d] 60% recovery of **1i**. [e] 59% recovery of **1g**.

The use of high-boiling solvents (xylenes, 1,1,2,2-tetrachloroethane, and DMF), but with more concentrated solutions (ca. 1.0 M) than before, was then revisited. For dienes **1a** and **1b**, a steady improvement in the yield was observed in going from no solvent (28% and 36%) to xylenes (32% and 48%) and then 1,1,2,2-tetrachloroethane (40% and 70%). In changing to a much more polar solvent (DMF), the yield of **16a** dropped off considerably (12%), and DMF was consequently excluded from further study. The use of 1,1,2,2-tetrachloroethane also resulted in significant yield enhancements for xanthones **16c** (90%) and **16d** (98%).

Dienes **1e** and **1f** behaved somewhat differently. Upon treatment of the crude mixtures with $Et_2O{\cdot}BF_3$, a yellow byproduct, **19e** (10%) and **19f** (4%), formed alongside the

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(16) A stepwise reaction (Michael/Mannich) cannot be ruled out at this time, but we currently favor the asynchronous IEDDA pathway. More detailed commentary on this subject will be forthcoming.

desired xanthones **16e** (18%) and **16f** (38%). The structure of **19e** was determined using single-crystal X-ray analysis, and that of **19f** was assigned by analogy. The aryl substituted dienes **1g**−**i** exhibited little or no reactivity toward TME (**9**). Slow, unproductive consumption of these dienes was observed under prolonged heating.

A proposed reaction landscape that is consistent with the observations is presented in Scheme 4. IEDDA reaction between **1** and **9** at 135 °C affords adducts **17**, which can undergo 1,2-elimination of methanol to afford dienes **18**. This elimination is proposed to occur first because the C(2) hydrogen atom should be the most acidic,[17] and by inspection, an *antiperiplanar* orientation of the C−H and one of the adjacent C−O bonds looks to be easily achievable. Dienes **18** then have two pathways available to them, namely the 1,2-elimination of a second molecule of methanol[18] to afford xanthones **16** and rearrangement to give dienes **15**.[19] Rearrangement could conceivably occur either through a ^{1,5}H shift[20] or an acid- or base-catalyzed tautomerization. Regardless of which mechanism operates, the partial aromaticity of the 4-pyrone ring[21] in **15** may provide some incentive for rearrangement. Whatever the case, AM1 calculations[22] predict that the lowest energy conformer of **15e** is ca. 4 kcal/mol more stable than that of **18e**. The reluctance of the rearranged dienes **15** to undergo what must surely be a very exothermic elimination of methanol under quite forcing conditions (135 °C) is somewhat surprising, even considering that the C(3)-H bond of **15d** is oriented essentially *gauche* to both C(4)-O bonds (disfavoring E2-like elimination) in the crystal (see inset in Scheme 3). Treatment of dienes **15** with $Et_2O{\cdot}BF_3$ proceeds smoothly under mild conditions, presumably because an E1-like mechanism becomes available.

The formation of byproducts **19e**,**f** in the reactions of **1e**,**f** with **9** is difficult to explain without invoking the involvement of dienes **18e**,**f**. Whether these dienes are present at the end of the thermal stage of the reaction or they come from **15e**,**f** or **17e**,**f** upon treatment with $Et_2O{\cdot}BF_3$, the conversion of **18e**,**f** to **19e**,**f** can be accounted for by a BF_3-catalyzed tautomerism involving the transfer of a methyl group from one end of a vinylogous ester to the other (see the Supporting Information for a proposed mechanism). Why the byproduct formed only in the reactions of **1e**,**f** is unclear.

Like xanthone itself,[23] xanthones **14a**−**f** and **16a**−**h** exhibited very weak fluorescence ($\phi_{em} < 10^{-3}$). However, the behavior of the 2-arylxanthones **14g**−**i** was more interesting (see the Supporting Information). As the electron-donating ability of the aryl substituent increased, the lowest energy absorption bands of **14g**−**i** moved to higher energy and the emission bands moved to lower energy with a concomitant increase in intensity, which is inconsistent the "energy gap law".[24] Furthermore, λ_t became larger (λ_t = 1680, 2390, 3030 cm^{-1} for **14g**−**i**, respectively) as calculated from the increasing Stokes shifts.[25] By comparison, λ_t ranges from 1420 to 1720 cm^{-1} for **14a**−**f** and **16a**−**h**. Quantum yields (ϕ_{em}) for **16h**, **14h** and **14i** are 0.007, 0.07, and 0.13, respectively. A tentative interpretation of this data is that charge transfer becomes more significant along the series **14g**−**i**, which increases λ_{vib} due to population of the π^* orbitals of the acceptor (the xanthone moiety) and λ_o[24] due to changes in the dipole moment on formation of the charge-transfer excited state.[26] A Franck−Condon line-shape analysis of the emission spectra and lifetime studies are currently underway to test this hypothesis.

In summary, IEDDA reactions between dienes **1** and dienophiles **8** and **9** afford a range of 4-methoxy- (**14)** and 3,4-dimethoxyxanthones (**16**) with useful functionality at the 2 position. Work aimed at the use of this methodology for the construction of more elaborate xanthonoid systems and new xanthone-based fluorophores is underway.

Acknowledgment. Financial support of this work from the Natural Sciences and Engineering Research Council (NSERC) of Canada is gratefully acknowledged. Dr. D. W. Thompson (Memorial University) is thanked for valuable discussions.

Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for **1a**−**i**, **14a**−**i**, **15d**, **16a**−**h**, and **19e**,**f**, UV−vis spectra and fluorescence spectra for **14a**−**i** and **16a**−**h**, crystal structure data and CIF files for **15d** and **19e**, and a proposed mechanism for the conversion of **18e**,**f** to **19e**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For example, in the case of **17b**, this H atom is part of a vinylogous malonate, i.e., glutaconate, system.

(18) On the surface, this elimination doesn't appear to be disfavored in any way. In an AM1-calculated (ref 21) structure of **18f**, a H−C−C−O dihedral angle of 164° at the site of elimination is predicted.

(19) The question arises of whether the reactions of dienes **1** with enamine **8** involve a similar rearrangement. Based on the evidence that is currently available, this possibility cannot be discounted.

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(21) (a) Zborowski, K.; Ryszard, G.; Proniewicz, L. M. *J. Phys. Org. Chem.* **2005**, *18*, 250. (b) Lumbroso, H.; Cure, J.; Evers, M.; *Z. Naturforsch. A* **1986**, *41*, 1250.

(22) Chem3D, Version 5.0.

(23) (a) Heinz, B.; Schmidt, B.; Root, C.; Satzger, H.; Milota, F.; Fierz, B.; Kiefhaber, T.; Zinth, W.; Gilch, P. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3432. (b) Murov, S. L.; Carmichael, I.; Hug, G. L. *Handbook of Photochemistry*; Marcel Dekker: New York, 1993.

(24) The intensity changes indicate that there are other (yet to be identified) nonradiative pathways that lower f_m.

(25) Stokes shifts are given by $E_{abs} - E_{em} = 2l_t$, where l_t is the total reorganization energy, which is a linear combination of the vibrational (l_{vib}) and solvent reorganization (l_o) energies, respectively.

(26) Chen, P.; Meyer, T. J. *Chem. Rev.* **1998**, *98*, 1439.