JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Cycloaddition Reactions of Indanedioneketene with Electron-Rich Dienophiles: An Experimental and a Theoretical Study

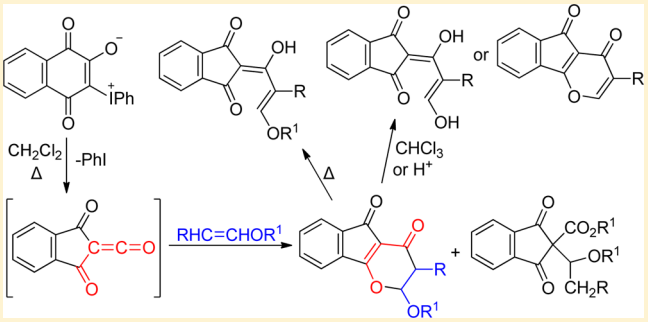
Elizabeth Malamidou-Xenikaki,*[,†] Spyros Spyroudis,[†] Erifili Tsovaltzi,[†] and Evangelos G. Bakalbassis[‡]

[†]Laboratory of Organic Chemistry, School of Chemistry, Faculty of Sciences, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece

[‡]Laboratory of Applied Quantum Chemistry, School of Chemistry, Faculty of Sciences, Aristotle University of Thessaloniki, P.O. Box 135, 54124 Thessaloniki, Greece

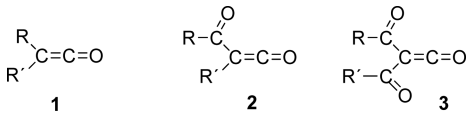
Supporting Information

ABSTRACT: Thermal decomposition of the phenyliodonium ylide of lawsone gives rise to a highly reactive cyclic α,α′-dioxoketene, indanedioneketene, which reacts with electron-rich dienophiles such as enol ethers to afford [4 + 2] cycloadducts. The initially formed 2,3-dihydro-2-alkoxy-indeno[1,2-*b*]pyrano-4,5-diones are labile compounds since through an opening of the pyranone ring upon heating they easily tautomerize to alkoxyallylidene-indenedione derivatives and under acid-catalysis they are additionally transformed to 2-(1,3-dihydroxyallylidene)-1*H*-indene-1,3(2*H*)-dione or by loss of alcohol to indeno[1,2-*b*]pyran-4,5-diones. A DFT study explains the polar nature of the cycloaddition reaction, the observed reactivity and suggests a possible mechanism operating in these reactions.



INTRODUCTION

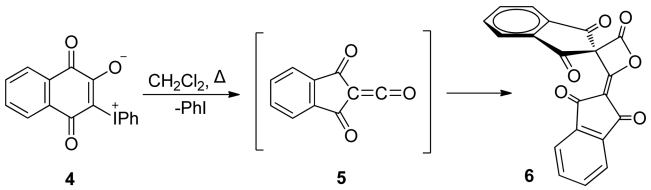
Ketenes **1** are known for more than a century now as important building blocks in organic synthesis.[1] These versatile compounds exhibit an interesting reactivity depending on the substituents on the ketene moiety. Compounds bearing an oxo group next to the ketene moiety, α-oxoketenes, **2**, constitute a special class of ketenes, with special features in their chemistry, which has been reviewed some years ago.[2,3] In contradiction to the great variety of α-oxoketenes, only a few examples of their dioxo-substituted counterparts, α,α′-dioxoketenes, **3**, have been reported in the literature.[4−8]



In the course of our studies on the chemistry of zwitterionic iodonium compounds,[9] we found that certain cyclic α,α′-dioxoketenes are the result of the thermal decomposition of aryliodonium ylides of hydroxyquinones. Such ketenes are not isolable, but their formation can be safely deduced from the products of their reaction with various reagents, mainly nucleophiles.

The most well-studied ketene of this kind is indanedioneketene (**5**), resulting from the thermal degradation of phenyliodonium ylide of lawsone (**4**) (Scheme 1). Indanedioneketene (**5**) cannot be isolated as it is transformed quantitatively to the spiro oxetanone dimer **6** under the experimental conditions.[10,11] Both ring contraction of ylide **4** to indanedioneketene (**5**) as well as dimerization of the latter to oxetanone **6** have been investigated theoretically.[12,13]

Scheme 1. Thermal Degradation of Phenyliodonium Ylide of Lawsone (4) to Indandioneketene (5) and Dimerization of the Latter to the Oxetanone Derivative 6



Oxetanone **6** is a labile compound and reacts further with amines affording enolic structures of iminoesters and iminoamides,[11] which can be further converted to enamino derivatives of 1,3-dioxoindane-2-carboxylic acid[14] and to fused indeno-1,4-diazepinones,[15] respectively. Oxetanone **6** also reacts with aminopyridines to afford indeno[1,2-*d*]pyrido[1,2-*a*]pyrimidines, compounds acting as potential receptor tyrosine kinase inhibitors.[16]

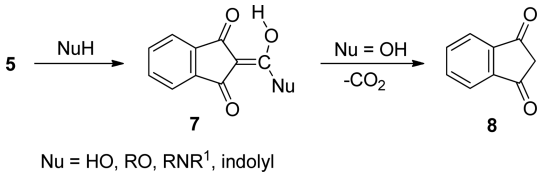
In the presence of nucleophiles, ketene **5** can be trapped affording interesting derivatives. With amines it gives the enolamides[17] **7** and the corresponding enolamide derivatives upon reaction with amino esters, amino acids, amino alcohols, and urea.[18] It also acylates indole derivatives and other C-

Received: December 22, 2015
Published: February 26, 2016

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

nucleophiles, such as pyrrole, furan, and enamines.[10] Reaction of **5** with alcohols leads to the corresponding esters, while in the presence of water, indanedione (**8**), resulting from decarboxylation of the intermediate highly unstable acid,[9] is the only product (Scheme 2).

Scheme 2. Trapping of Indanedioneketene (5) with Nucleophiles

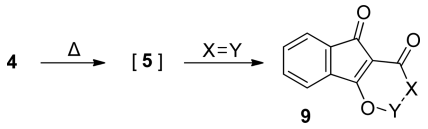


It is obvious that indanedioneketene, although not isolable, is a versatile building block for the construction of more complex structures bearing the indanone moiety. For this reason we investigated its reactivity with dipolarophiles, both experimentally and theoretically, and present our results here.

RESULTS AND DISCUSSION

Chemistry. Indanedioneketene (**5**) is formed in refluxing suspensions of phenyliodonium ylide of lawsone (**4**) in CH_2Cl_2, and in the absence of nucleophiles, it is converted quantitatively to the oxetanone dimer **6**. For this reason the dipolarophile X = Y must be present from the beginning of the thermal degradation of ylide **4** to ketene **5** for the isolation of addition products of the general structure **9** (Scheme 3).

Scheme 3. General Scheme for the Cycloaddition Reaction of Indanedioneketene (5) with Dipolarophiles X = Y

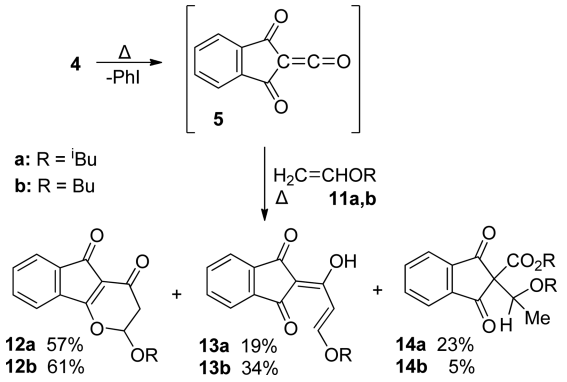


A first attempt to obtain a cyclization product using cyclohexene (**10**) as a dienophile was unsuccessful despite the different reaction conditions applied (reflux in cyclohexene, use of CH_2Cl_2 or $CHCl_3$ as co-solvents, irradiation in a microwave (MW) oven 130 °C/15 min, 140 °C/20 min, 150 °C/15 min). The main product in most attempts was oxetanone **6**, indicating that the thermally produced indanedioneketene reacts with the ethylenic bond of a second ketene molecule rather than with the double bond of cyclohexene. Analogous results were obtained from the thermal degradation of ylide **4** in the presence of a number of acetylene derivatives such as phenylacetylene, trimethylsilylacetylene, bis(trimethylsilyl)acetylene, and 3-hexyne.

Finally, indanedioneketene (**5**) reacted with more electron-rich dienophiles, such as enol ethers. When the degradation of ylide **4**, and hence the formation of indanedioneketene (**5**), took place in refluxing isobutyl vinyl ether (**11a**) (bp 82−83 °C) or butyl vinyl ether (**11b**) (bp 94 °C) for 90 or 35 min, respectively, the products **12**−**14** depicted in Scheme 4, were isolated. The end of the reactions was signaled by the clearness of the initial suspension, indicating the decomposition of the insoluble reactant ylide **4**.

It must be noted that the isolation of acetals **12** was possible only through their partial crystallization from the reaction

Scheme 4. Reaction of Indanedioneketene (5) in Refluxing Alkyl Vinyl Ethers



mixture, since passing through a chromatography column resulted in their decomposition. The indanedione derivatives **14** and part of products **13** were obtained by column chromatography of the residue, although compounds **13** were sometimes successively crystallized. Products **13** are relatively sensitive to acidic environment, and, depending on the rate of passing through the column or the type of elution solvent, they can be partly retained in the column. So, the separation and isolation method is one reason for the variation in the isolated yields obtained from different experiments, and the second one being the reaction course itself as described later. The actual overall yields of products **12** and **13** were estimated on the base of integrals in the ^1H NMR spectra of the corresponding reaction mixture, and the calculated yields are depicted in Scheme 4.

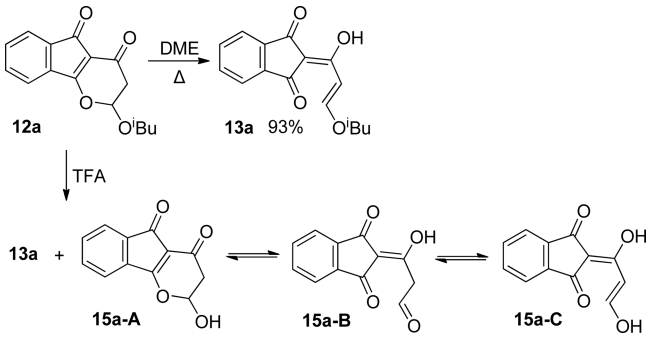
Products **12** seem to be the initial [4 + 2] adducts. A limited number of 2-alkoxy-2,3-dihydro-pyran-4-ones analogous to the **12** structure have been reported to arise from the reactions of some other α-oxo- or α,α′-dioxoketenes with vinyl ethers.[19−24] Upon heating, products **12** partially tautomerize to the most stable alkoxyallylidene-indenediones **13**, and during work up they are converted partly to tautomers **13** and hydrolyze to hemiacetal **15**. This assumption was verified by some independent reactions of the isolated **12a**. Upon refluxing in dimethoxyethane, DME, **12a** entirely isomerized to **13a** (yield 93%), whereas upon prolonged staying in chloroform solution or upon treatment with TFA in dichloromethane solution at room temperature (rt), compound **13a** and the hemiacetal **15a** were isolated in a ratio ranging from 1:0.1 to 1:2 depending on the reaction conditions (Scheme 5).

Regarding the fourth reaction product, indanedione carboxylates **14**, a plausible reaction pathway might involve initial formation of esters **16** from the reaction of ketene **5** with the corresponding alcohol produced during the reaction course or present even in small amounts in the reactant-solvent vinyl ether. The proton on the indanedione carbon, being highly acidic due to the three adjacent carbonyl groups, protonates the vinyl ether to form an oxonium intermediate **18**, which couples with the anionic species **17** to afford the isolated products **14** (as it is exemplified for the reaction with isobutyl vinyl ether, Scheme 6).

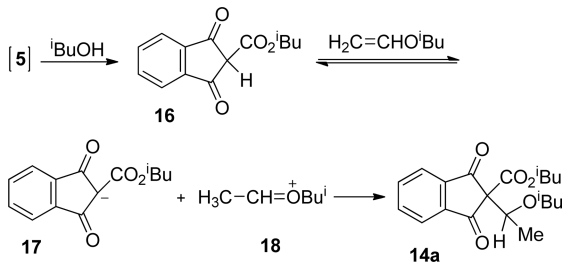
In refluxing ethyl vinyl ether (**11c**) (bp 33 °C), ylide **4** remained practically unchanged. When CH_2Cl_2 was used as a co-solvent, the only isolable products were 2-(1-hydroxy-3-hydroxyallylidene)-1*H*-indene-1,3(2*H*)-dione (**15a**, 19%), ester **14c** (9%), and indanedione (**8**, 32%), whereas 35% of the ylide

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Scheme 5. Thermal Isomerization of 12a to 13a and Transformation to 15a by Acid-Catalyzed Elimination of Isobutanol

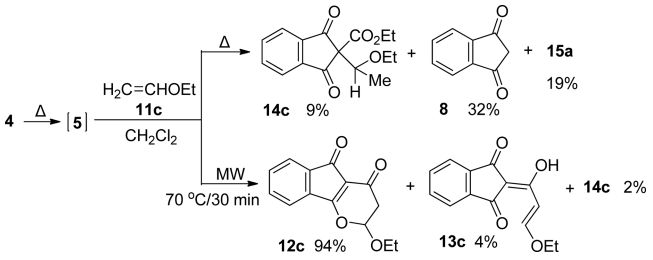


Scheme 6. Reaction Pathway for the Formation of 14



remained unchanged (Scheme 7). The above results indicate that elevated temperatures are necessary for the cycloaddition

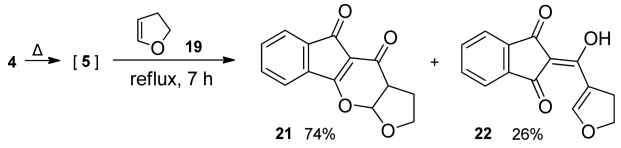
Scheme 7. Reaction of Ketene 5 with Ethyl Vinyl Ether



reaction. When the same reaction was performed in a MW oven (70 °C, 11 min), using CH_2Cl_2 as solvent, a large amount of ylide **4** remained unchanged, but compound **12c** was detected by ^{1}H NMR in the reaction mixture together with small amounts of the ester **14c** and indanedione (**8**). Upon prolonged MW irradiation (70 °C, 30 min), the reaction was completed, as indicated by the clarification of the reaction mixture. Cycloadduct **12c** was estimated by ^{1}H NMR as the main product (yield 94%) in the reaction mixture; the other two being **13c** and ester **14c** in 4% and 2% yields, respectively. The highly labile compound **12c** was crystallized by treatment of the concentrated reaction mixture with petroleum ether and was immediately decomposed either in solution or in solid state to **15a**.

The reaction with cyclic enol ethers, such as 2,3-dihydrofuran (**19**) and 3,4-dihydro-2*H*-pyrane (**20**), followed essentially the same reaction pathway. Refluxing of ylide **4** in excess of 2,3-dihydrofuran (bp 54−55 °C) for 7 h, until clearness of the reaction mixture, resulted in products **21** and **22** (Scheme 8) in yields 74% and 26%, respectively, estimated by ^{1}H NMR. Product **21** was partially crystallized (yield 37%) from the

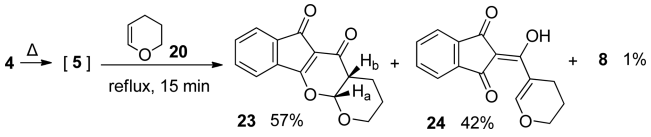
Scheme 8. Reaction of Ketene 5 with 2,3-Dihydrofuran



reaction mixture, whereas compound **22** was isolated (yield 22%) through column chromatography of the residue.

Analogous results were obtained from the reaction with 3,4-dihydro-2*H*-pyran (**20**) (Scheme 9). Refluxing of ylide **4** in 3,4-

Scheme 9. Reaction of Ketene 5 with 3,4-Dihydro-2*H*-pyran



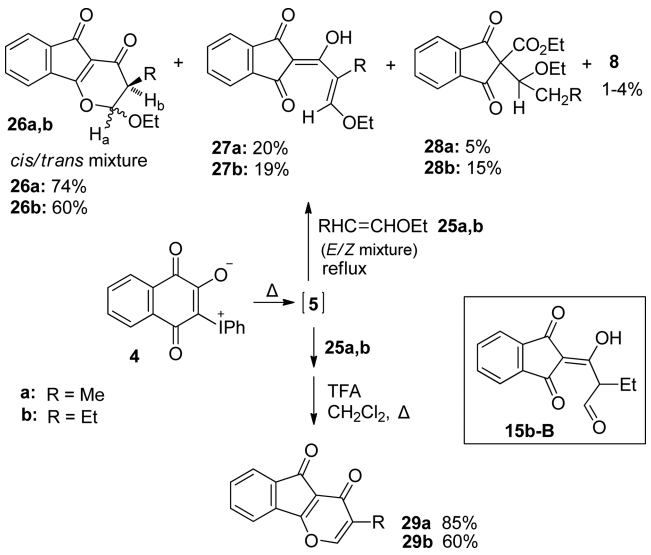
dihydro-2*H*-pyran (bp 83−86 °C) for 15 min gave a mixture of the initial cycloaddition product **23** (57%) and its thermal transformation isomer, the acylated dihydropyran derivative **24** (42%) accompanied by traces of indandione (1%) as estimated by ^{1}H NMR. Concentration of the excess dihydropyran, followed by treatment of the reaction mixture with petroleum ether resulted in the precipitation of a nonseparable mixture of **23** and **24**. Passing this mixture through a chromatography column only gave pure product **24**. Aiming to prevent the transformation of acetal **23** to the pyranone ring opening product **24**, the reaction was run at a lower temperature (55−60 °C). Under these conditions, the reaction lasted 7 h until clarification of the starting suspension and resulted to ylide **4** decomposition products, confirming once again the necessity of relatively elevated temperatures for the successful outcome of the cycloaddition reaction. The temperature required in the case of 3,4-dihydro-2*H*-pyran is obviously higher than that required for the reaction of 2,3-dihydrofuran.

The reactions with 2-substituted ethyl vinyl ethers, such as 1-ethoxyprop-1-ene (**25a**) (bp 67−71 °C) or 1-ethoxybut-1-ene (**25b**) (bp 94−95 °C), afforded the cycloaddition products **26**, their tautomers **27**, together with esters **28**, in yields (estimated by ^{1}H NMR) depicted in Scheme 10. Specifically, from the reaction of ylide **4** with excess of refluxing **25a** (mixture of *E*:*Z* stereoisomers ∼1:2) for 4 h, the acetal **26a** was formed as a nonseparable mixture of diastereoisomers in a ratio 0.63:1.00 ($J_{a,b}$ = 3.4 and 5.8 Hz, respectively) whereas the ethoxyallylidene-indanedione **27a** was obtained exclusively in the *E*-configuration as defined by a NOESY experiment. This ratio for the stereoisomers of **26a**, which does not reflect the ratio of isomers of the starting material, indicates that either the reaction of one isomer **25a**—presumably the *Z* one—is less favorable, probably due to steric interactions developing in the transition state (kinetic control) or one of the stereoisomers **26a** is more easily converted to the tautomer *E*-**27a**. Furthermore, the formation of products **27**, exclusively as *E*-stereoisomers, from the ring opening reaction of the mixture of diastereoisomers **26** seems interesting and could be attributed to increased steric effects in the corresponding *Z*-**27** isomers.

Similarly, an impartible mixture of the two diastereoisomers **26b** (ratio 0.85:1.00, $J_{a,b}$ = 3.4 and 3.5 Hz, respectively) was formed from the reaction (reflux for 25 min) of ylide **4** with excess of 1-ethoxybut-1-ene (mixture of *E*:*Z* stereoisomers

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Scheme 10. Reaction of Ketene 5 with 1-Ethoxyprop-1-ene and 1-Ethoxybut-1-ene

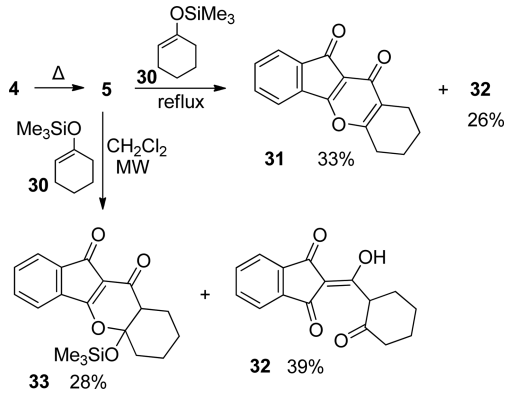


~1.00:1.45) together with **27b**, isolated in the *E*-form, and ester **28b**. An effort to separate **26b** from the reaction mixture through crystallization (CH_2Cl_2/petroleum ether) was fruitless leading to the corresponding hemiacetal **15b**, appearing in solution (^{1}H NMR) as tautomer **15b-B**.

Addition of trifluoroacetic acid in a gently heated dichloromethane solution of the appropriate reaction mixture afforded methyl- and ethyl-substituted indeno-pyranones **29a** and **29b** in 85% and 60% yields, isolated by crystallization and column chromatography, respectively (Scheme 10).

The reaction of ylide **4** in refluxing (cyclohexenyloxy)-trimethylsilane (**30**) (bp 64−65 °C) for 75 min resulted in a complex mixture from which the isolation of any solid product was impossible. Also, the estimation of structure and yield of the products from the complicated ^{1}H NMR spectrum of the reaction mixture was impracticable. Upon separation of the mixture with column chromatography, tetrahydroindeno-chromenedione **31** and compound **32** in 33% and 26% yields, respectively, were isolated (Scheme 11). Compound **32** was isolated as a hydrate (**32**·H_2O). The reaction with cyclohexenyloxy(trimethyl)silane was also performed in CH_2Cl_2 under MW irradiation, at 90 °C for 3 min, to afford the trimethylsilyloxy-chromenedione derivative **33**, (28% yield)

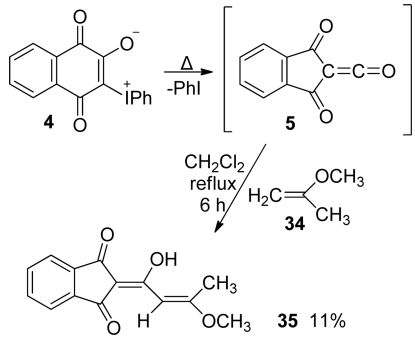
Scheme 11. Reaction of Ketene 5 with (Cyclohex-1-en-1-yloxy)trimethylsilane



and tetraoxo compound **32** (hydrate form, 39% yield) isolated by crystallization and column chromatography, respectively.

Unsurprisingly, ylide **4** remained unchanged at a very high percentage (~95%) when it was refluxed in suspension with the low boiling point, 34−36 °C, 2-methoxyprop-1-ene (**34**). When the reaction was repeated in refluxing dichloromethane, (*E*)-2-(1-hydroxy-3-methoxybut-2-en-1-ylidene)-1*H*-indene-1,3(2*H*)-dione (**35**) was isolated in almost 11% yield (Scheme 12), whereas 80% of ylide **4** was also recovered unchanged.

Scheme 12. Reaction of Ketene 5 with 2-Methoxyprop-1-ene



Finally, the reaction of ylide **4** with 2-methoxy-3,4-dihydro-2*H*-pyran (**36**) (bp 125−127 °C) was studied. Heating of a suspension of ylide **4** and enol ether **36** at 80 °C, until clearness of the reaction mixture, resulted in indenopyranopyrandione **37** and compound **38** (Scheme 13) in yields 25% and 38%, respectively, estimated by ^{1}H NMR.

As seen from the results above, reaction temperatures exceeding that of the ylide's **4** decomposition, and consequent ketene **5** formation, are required for the cycloaddition reactions. However, the appropriate temperature varies and in any case depends on the structure of each dienophile. The temperature at which the reaction takes place is also critical for the stability of the initial cycloadducts. Higher temperatures appear to favor the tautomerization through opening of the pyranone ring (25% conversion of the initial **12a** to **13a** in case of the reaction of **11a** (temp. 83 °C) compared to the 36% conversion of **12b** to **13b** in case of the reaction of **11b** (temp. 94 °C). A similar conclusion is reached by comparing the results of the reactions of dihydrofuran **19** and dihydropyran **20**. The conversion of **23** to **24** approaches a percentage of 42%, compared to 26% conversion of **21** to **22**, as a result of carrying out the former reaction at a temperature higher by 30°. Also, in the reactions of **11a** and **20**, carried out under comparable temperatures, the transformation of the initial cycloadduct to the respective ring opening product appears to be more favorable in the case of the cyclic enol ether **20**.

Based on the above observations and aiming at a more thorough study of these cycloaddition reactions of indanedioneketene (**5**), their replication was designed under similar and comparable conditions, so that safer conclusions could be drawn regarding the effect of the dienophile's structure on the reaction outcome and the relative stability and efficiency to transform of the resulting products. Another objective was to find distinct conditions for the quantitative formation and isolation of the initial cycloadduct or its open-ring tautomerized form in each discrete case. The MW irradiation (70 °C for 30 min) was the first method tested due to its successful application in the formation of product **12c**, almost exclusively,

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Scheme 13. Reaction of Ketene 5 with 2-Methoxy-3,4-dihydro-2*H*-pyran

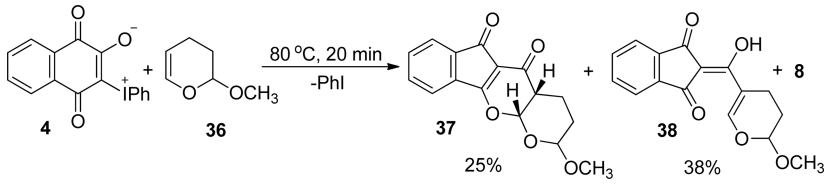


Table 1. Results from the Reactions of Ylide 4 with Enol Ethers Under MW Irradiation

entry	enol ether	reaction conditions[a]	initial cycloadduct (%)	alkoxyallylidene-indenedione (%)	indanedione-2-carboxylate (%)	indanedione **18** %	unreacted starting ylide **4** %
1		**A**	**12a** (78)	**13a** (11)	**14a** (11)	0	0
2	**11a**	**B**	**12a** (81)	**13a** (13)	**14a** (6)	0	0
3		**C**	**12a** (2)	**13a** (70)	**14a** (28)	0	0
4		**A**	**12b** (79)	**13b** (11)	**14b** (10)	0	0
5	**11b**	**B**	**12b** (83)	**13b** (12)	**14b** (4)	0	0
6		**C**	**12b** (0)	**13b** (75)	**14b** (25)	0	0
7		**A**	**12c** (94)	**13c** (4)	**14c** (2)	0	0
8	**11c**	**B**	**12c** (90)	**13c** (8.5)	**14c** (1.5)	0	0
9		**C**	**12c** (0)	**13c** (74)	**14c** (26)	0	0
10		**A**	**21** (22)	**22** (60)	–	1	16
11	**19**	**B**	**21** (25)	**22** (75)	–	0	0
12		**C**	**21** (0)	**22** (94)	–	6	0
13		**A**	**23** (40)	**24** (48)	–	7	5
14	**20**	**B**	**23** (29)	**24** (68)	–	3	0
15		**C**	**23** (0)	**24** (89)	–	1.5	0
16		**A**	**26a** (73)[b]	**27a** (14)	**28a** (5)	8	0
17	**25a** (*E*/*Z* 1:2)	**B**	**26a** (80)[c]	**27a** (11)	**28a** (4)	4	0
18		**C**	**26a** (10)[d]	**27a** (74)	**28a** (14)	2	0
19		**A**	**26b** (54)[e]	**27b** (18)	**28b** (12)	16	0
20	**25b** (*E*/*Z* 1:1.45)	**B**	**26b** (57)[f]	**27b** (11)	**28b** (9)	23	0
21		**C**	**26b** (0)	**27b** (60)	**28b** (30)	10	0
22	**34**	**A**	–	**35** (98)	–	2	0
23		**B**	–	**35** (100)	–	0	0
24		**A**[g]	**33** (9)	**32** (49)	–	4	35
25	**30**	**B**	**33** (48)	**32** (48)	–	3	0
26		**C**[h]	**33** (0)	**32** (32)	–	6	0
27		**A**	**37** (26)	**38** (53)	–	5	–
28	**36**	**B**	**37** (10)	**38** (64)	–	8	–
29		**C**	**37** (0)	**38** (87)	–	4	–

[a]**A**: MW irradiation, 70 °C/30 min. **B**: MW irradiation, 100 °C/3 min. **C**: MW irradiation, 140 °C/20 min. [b]Mixture of diastereoisomers 1:1.23. [c]Mixture of diastereoisomers 1:1.67. [d]Mixture of diastereoisomers 1:1.17. [e]Mixture of diastereoisomers 1:1.24. [f]Mixture of diastereoisomers 1:0.96. [g]Product **31** in 3% yield was also detected. [h]Product **31** (62% yield) was also isolated.

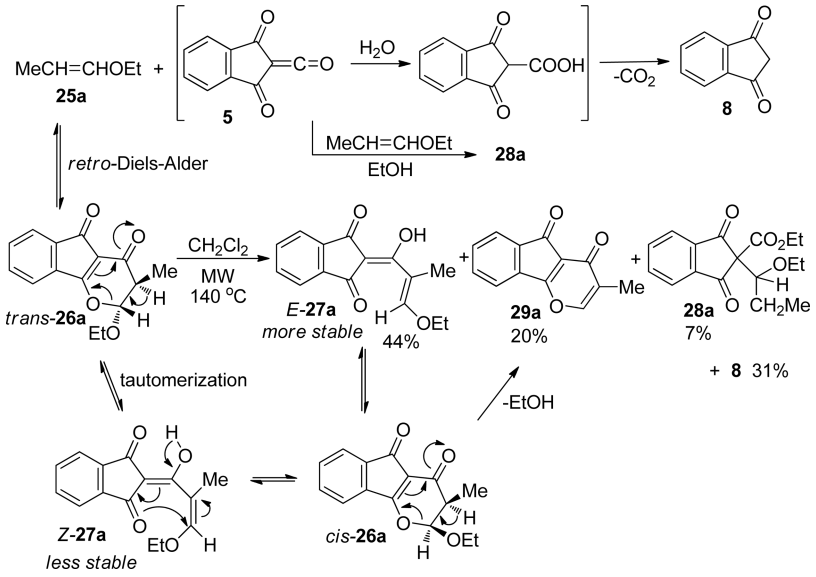
from the reaction of **11c**. The mixture of ylide **4** with **11b** was also irradiated with MW at 100 °C for 10 min. Under these conditions, the ylide reacted quantitatively, but the initial adduct **12b** remained partly unchanged. Irradiation of the same reaction mixture in a MW oven at 140 °C for 20 min gave compound **13b** as the main product. After this brief exploratory effort, the conditions that finally were considered suitable to be applied are summarized in the following: MW irradiation at (i) 70 °C for 30 min, (ii) 100 °C for 3 min, and (iii) 140 °C for 20 min. The conditions finally implemented for each dienophile are listed in the Table 1 along with the product yields in each case.

From the results depicted in Table 1 it is clear that the open-chain unsubstituted or *β*-substituted vinyl ethers **11** and **25** react efficiently at 70 °C. The resulting cycloadducts **12** and **26** are proved stable enough under these conditions transforming to **13** and **27**, respectively, at a very small percentage (entries 1, 4, 7, 16, 19). Conversely, the initial cycloadducts **21**, **23**, and **37** derived from the reactions of the cyclic enol ethers **19**, **20**, and **36** are more efficiently transformed to their tautomers **22**, **24**, and **38**, respectively (entries 10, 13, 27). Furthermore, in the cases of the *α*-substituted and *α*,*β*-disubstituted enol ethers **34** and **30**, the initial cycloadducts are proved unstable enough, transforming to the corresponding open-ring tautomers **35** and **32** exclusively in the former and to an extent of 84% in the latter case (entries 22, 24).

For all the reactions contacted at 100 °C, the extent of tautomerization of the initial cycloadducts derived from both the reactions with open-chain unsubstituted or *β*-substituted vinyl ethers **11** or **25** and dihydrofuran (**19**) is almost the same with the previous one observed in the reactions done at 70 °C (entries 2, 5, 8, 11 in comparison with entries 1, 4, 7, 10), but it is sensibly increased in the case of dihydropyran (compare entries 14 and 13). This is rather indicative of a relative difficulty in the transformation of **23** to **24** where more vigorous conditions are required.

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Scheme 14. Conversion of Dihydroindeno-Pyrandione 26a to *E*-27a and 29a



It should be noted that in all cases where cycloadducts were the main products or were formed in high yields (entries 1, 2, 4, 5, 7, 8, 16), they were isolated through crystallization from the reaction mixture, by treatment with petroleum ether or ethyl ether/petroleum ether or dichloromethane/petroleum ether, and could be kept for a long time in the freezer. The crystallization of one isomer **26a** ($J_{a,b}$ = 5.8 Hz) in pure form was also achieved by treatment of the reaction mixture with ethyl ether/petroleum ether. In contrast, the isolation of cycloadduct **26b** was proved unattainable due to its instability. The isolation of the initial cycloadducts was also impossible in all cases where the reaction mixtures contained large amounts of the pyranone ring-opening products (entries 10, 11, 13, 14, 25). Of interest is the crystallization of pure compound **32** (entries 24, 25) instead of its hydrate form which is usually isolated whenever this compound passes through a chromatography column.

Upon MW irradiation at 140 °C for 20 min, almost in all cases, the reactions resulted quantitatively to the open-ring products except from the reaction of trimethylsilyloxycyclohexene (entry 26) in which the main product was compound **31**, derived obviously by elimination of Me_3SiOH from the initial adduct **33**. Generally, a considerable increase in yields of the indanedione-2-carboxylates **14a−c** and **28a,b** was observed (entries 3, 6, 9, 18, 21) that could be attributed to both the hydrolysis of the reagent enol ethers or a side retro-Diels−Alder (DA) reaction facilitated under the intense conditions applied (see later in Scheme 14). Therefore, under these conditions, the tautomerized open-ring products **13a−c**, **22**, **24**, **27a**, **35**, and **32** (entries 3, 6, 9, 12, 15, 18, 23) with very interesting structure can be formed almost quantitatively and can be isolated by crystallization. The only exception is product **27b** which is separated from the coexisting **28b** by column chromatography.

The isolation of one isomer **26a** in pure form provided us the opportunity for a thorough study of the tautomerization reaction of **26a**. Specifically, MW irradiation of **26a** (mixture of isomers with $J_{a,b}$ = 3.4 and 5.8 Hz ~ 0.68:1) in CH_2Cl_2 solution at 140 °C for 20 min resulted in the formation of *E*-**27a** (yield 43%). In addition, the reaction mixture contained a significant amount (~43%) of indanedione (**8**), together with indenopyrandione **29a** and ester **28a**, each in yield 7%. About 15% of the starting **26a** was recovered unchanged as a mixture of isomers ~0.44:1. The reaction of the isolated pure isomer **26a** under MW irradiation at 140 °C for 25 min gave exactly the same products. In this case, the starting material was completely consumed, and the reaction mixture consisted of (*E*)-2-(3-ethoxy-1-hydroxy-2-methylallylidene)-1*H*-indene-1,3(2*H*)-dione (*E*-**27a**) (yield 44%), a large amount of indanedione (yield 29%) as well as 3-methylindeno[1,2-*b*]pyran-4,5-dione (**29a**) (yield 20%) and indanedione-2-carboxylate **28a** (yield 7%). The formation of the same products, and especially of *E*-**27a**, from the reaction of the two stereoisomers **26a** could be attributed to the thermal interconversion of the two isomers **27** (Scheme 14) and ultimately to the predominance of the more stable (less hindered) *E*-**27a** isomer product (thermodynamic control). This interconversion occurs probably through an equilibrium of the initial cycloadducts **26a** and **26b**. Cycloadduct *cis*-**26a** is the only isomer that bears an ethoxy group positioned trans to the hydrogen on the adjacent carbon and thus is suitable for EtOH abstraction resulting to indenopyrandione **29a**. The origin of indanedione (**8**) and the ester **28a** could be attributed to a side retro-DA reaction. Hydration of the intermediate indanedioneketene (**5**) and subsequent decarboxylation of the highly unstable carboxylic acid **7** (Nu = OH) results in **8**, whereas the reaction of ketene **5** with EtOH and 1-ethoxyprop-1-ene (**25a**), following a mechanistic pathway analogous to that depicted in Scheme 6, gives compound **28a**.

Based upon the above experimental data, a theoretical approach for the investigation of (i) the global reactivity indexes of the reactants, (ii) the study of the feasible isomeric reaction channels, (iii) the energies, (iv) the geometries of the transition states, and (v) the possible mechanism operating in these reactions is presented herein, requiring for comparison, gas-phase calculations at the same temperature.

THEORETICAL STUDY

Computational Methods. All stationary points (reactants, loosely associated reactant dimers, hereafter denoted as dimers), transition states (TSs), and products found in the potential energy surfaces (PESs) were fully optimized at the

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

B3LYP/6-31G(d) level of theory,[25,26] because it was shown to be suitable for the analysis of the geometric and electronic properties of DA reactions.[27] Full geometry optimizations with tight convergence criteria and no symmetry constraints were performed for each species. The nature of the stationary points was determined in each case according to the number of the negative eigenvalues of the Hessian matrix (zero and one imaginary frequencies for the minima and TSs, respectively). The global electron density transfer (GEDT)[27b] at the TSs were analyzed with the natural bond order method.[28] All calculations were carried out using the Gaussian 09 programs suite.[29]

The determination of the appropriate TSs connecting reactants and products has been confirmed by intrinsic reaction coordinate (IRC)[30] calculations, during which intrinsic reaction paths (IRPs) were traced from the various transition structures to ensure that no further intermediates exist.[31]

It is worth mentioning here that B3LYP failed to afford significant activation energy differences (vide infra) for the two ortho enantiomeric derivatives of the reaction between indanedioneketene (**5**) and the isobutyl vinyl ether (**11a**). For this reason, we also used the BP86/6-31+G* method[32] for the optimization of the geometries of all stationary points, followed by single-point energy calculations at the MP2/6-31+G* level of theory, at the optimized gas-phase geometries. The latter method afforded significant corresponding activation energy differences for the two above derivatives of the same reaction. For this reason, the results of both methods are discussed throughout the paper. However, due to the absence of BP86 corresponding data in the literature, the B3LYP one is only presented in the paper. Most of the BP86 data is given in the Supporting Information.

Analysis of the Global Reactivity Indexes in the Ground State of the Reactants. It has been reported that both the global electrophilicity index, ω,[27b,33] along with the nucleophilicity index, N,[33c,27b] could be used to classify the dienes and dienophiles used in DA reactions. In particular, the former index categorizes the electrophiles on a single scale of electrophilicity; the latter one could describe the nucleophilic behavior of an organic molecule.

In order to establish the reactivity in the hetero-DA cycloaddition reactions under study, an analysis of the reagents based on DFT reactivity indices was performed. In Table 2, both the B3LYP global electrophilicity index (ω) along with the nucleophilicity index, N [referring to tetracyanoethylene (TCE), taking as a reference] of indanedioneketene (**5**), and the dienophiles such as enol ethers **11a**, **19**, **20**, *Z*-**25a**, *E*-**25a**, and cyclohexene (**10**) are shown. The BP86 indexes are given in Table S1.

Table 2. Electrophilicity (ω, eV) and Nucleophilicity, (N, eV) Indexes of Indanedione-Ketene (5), Enol Ethers 11a, 19, 20, *Z*-25a, *E*-25a, and Cyclohexene (10)

no.	ω	N
5	2.35	1.94
10	0.50	2.77
11a	0.42	3.21
19	0.36	3.56
20	0.37	3.40
E-**25a**	0.35	3.47
Z-**25a**	0.35	3.47

The molecules are shown in the table in decreasing order of the ω value. Indanedioneketene (**5**) appears at the top of this table, classified as a strong electrophile, while all of the enol ethers **11a**, **19**, **20**, *Z*-**25a**, *E*-**25a**, and cyclohexene **10** exhibit significantly lower ω values than **5**, classified as very low electrophiles.[33c] An examination of the nucleophilic N descriptor for these molecules clearly shows a relationship between the nucleophilicity and the nature of the reactants. As a matter of fact, we could distinguish three subgroups clearly differentiated: the ketene **5**, with N = 1.94 eV, cyclohexene (**10**), with N = 2.77 eV, and the enol ethers—classified as strong nucleophiles—exhibiting close to each other N values, ranging from 3.21 to 3.56 eV. In addition, there is a clear inverse relationship between the electrophilic ω and the nucleophilic N powers. Thus, along a DA reaction, **5** will act as electrophile, whereas **10** and all enol ethers act as nucleophiles, in clear agreement with the flux of the electron density transfer at the TSs (vide infra). Moreover, the large electrophilicity of the acceptor reagent **5**, (ω = 2.35 eV), is in line with a large reactivity toward all but one, (**10**), dienophiles under study (exhibiting large N values). This is in accord with both the relatively low calculated activation energies of the cycloadditions through a more polar process (vide infra, Table 3) and the experiment outcomes.

An analysis of ω and N for both pairs of reactants **5**/**10** and **5**/**20** could explain the reactivity of **5** in a DA reaction. In both cases, within the electrophilicity scale, **5** is located above both **10** and **20**, hence, it will act as electrophile, whereas both **10** and **20** will act as nucleophiles, in close agreement with the GEDT at the TSs (vide infra). Moreover, dihydropyran (**20**) is more nucleophilic than cyclohexene (**10**). Hence, the DA reaction between **5**/**20** will have a more polar character than that between **5**/**10**. This result is in very good agreement with (i) the lower activation energy calculated (see Table 3) for the more favorable DA reaction between **5**/**20** (11.5 kcal/mol), than for the one between **5**/**10** (20.2 kcal/mol), and (ii) the larger GEDT found in the former, 0.48 e, than at the latter, 0.25 e. The lowest value, corresponding to the reaction of **5** with the unsubstituted enol ether **11a**, seems strange, because both open chain β-substituted enol ethers, *Z*-**25a** and **5**/*E*-**25a**, present both lower ω and higher N values than that. Hence, these two should be expected to present the highest activation energy values. A possible explanation for this discrepancy could be the lower steric interactions in the reaction of **5** with the **11a**, compared to those with the *Z*-**25a** and *E*-**25a**. In addition, cycloaddition reactions will have a large polar character, as a result of the strong electrophilic character of the ketene and the strong nucleophilic character of the enol ethers.

A comparison between the B3LYP and BP86 (Table S1) ω and N values clearly shows that (i) the B3LYP ω values are almost the half of the BP86 ones, whereas the BP86 N ones are slightly larger than those of B3LYP, and nevertheless, (ii) both ω and N value trends in both methods are identical.

Study of the Feasible Regio- and Stereoisomeric Reaction Channels. The computational model corresponding to the reaction of **5** with **11a** is only presented herein for which, due to the asymmetry of both reagents, four routes are possible, related to the formulation of ortho and meta regio-isomeric products and the endo and exo approach modes. The endo and exo approaches produce pairs of enantiomeric cycloadducts corresponding to each of the ortho and meta mode (Scheme 15).

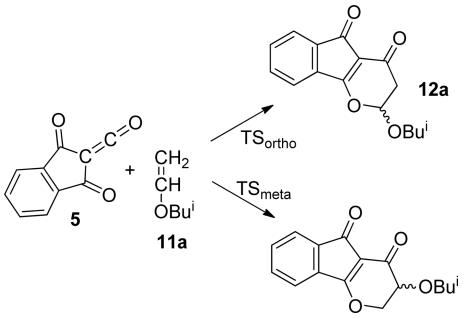
DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Table 3. B3LYP Calculated Total[a] (E, au) and Relative Energies (ΔE, kcal/mol) of the Stationary Points Involved in the DA Reactions of 5 with the Enol Ethers, along with GEDT (e) at the Corresponding TSs

reagents		TSs		cycloadducts			
no.	E	no.	E	$\Delta E^{\#}$	GEDT	E	ΔE
10	−234.6483375	TS**5**/**10**	−843.7441243	20.2	0.26	−843.8084662	−20.2
20	−270.5443817	TS**5**/**20**	−879.6540358	11.5	0.51	−879.7024366	−18.9
19	−231.2218122	TS**5**/**19**	−840.3365985	8.3	0.61	−840.3863604	−23.0
Z-**25a**	−271.7484267	TS**5**/*Z*-**25a**	−880.8634116	8.1	0.34	−880.9121124	−22.4
E-**25a**	−271.747812	TS**5**/*E*-**25a**	−880.8628439	8.1	0.32	−880.9108114	−22.0
11a	−311.0584225	TS**5**/**11a**	−920.1770359	5.9	0.28	−920.2249023	−24.2

[a]The total energy of ketene (**5**) is −609.1279369 au.

Scheme 15. ortho and meta Mode of the DA Reaction of Ketene 5 and 11a



Calculations have shown that of the four possible corresponding TSs of the reaction studied, being TS$_{ortho,endo}$, (hereafter denoted as TS$_{o\text{-}n}$), TS$_{ortho,exo}$ (TS$_{o\text{-}x}$), TS$_{meta,exo}$ (TS$_{m\text{-}x}$), and TS$_{meta,endo}$, (TS$_{m\text{-}n}$) (shown in Figure 1) the

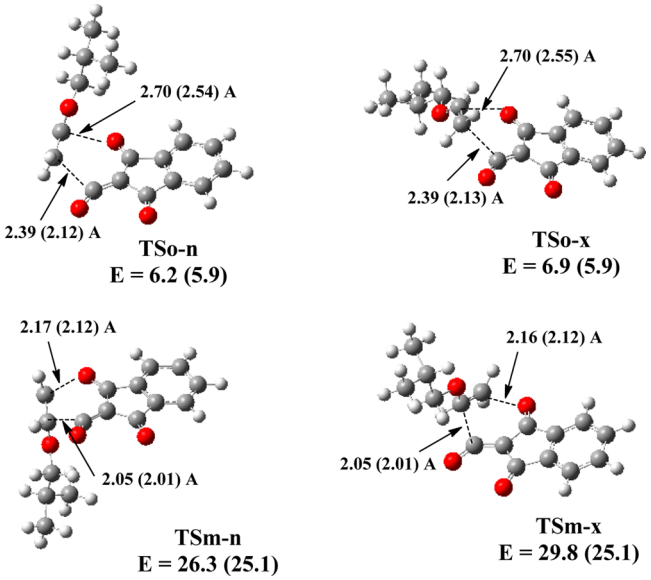


Figure 1. Four possible TSs involved in the polar DA reaction of **5** with **11a**. (B3LYP calculated values are given in parentheses. Distances are given in angstroms, energies in kcal/mol).

TS$_{o\text{-}n}$ presented the lowest activation energy at the BP86 level (6.2 kcal/mol), compared to 6.9 kcal/mol, for the TS$_{o\text{-}x}$ (see Tables S2 and S3). It is worth noting that contrary to BP86, B3LYP afforded identical $\Delta E^{\#}$ values (5.9 kcal/mol) for both TS$_{ortho}$. Moreover, both methods afforded much higher $\Delta E^{\#}$ values for both TS$_{meta}$, compared to those of the TS$_{ortho}$. These results are in excellent agreement with the experiment, showing that the ortho cycloadducts are isolated only. Moreover, an exhaustive study of the stationary points found on the potentional energy surface of the **5**/**11a** DA reaction showed one dimer, one TS$_{o\text{-}n}$, and the corresponding cycloadduct. Consequently, the same stationary points were located and characterized for all PESs studied at the BP86 level; one TS$_{o\text{-}n}$ and the corresponding cycloadduct at the B3LYP one.

The geometries of the above four TSs are given in Figure 1 for both methods. Despite the different geometries derived for the corresponding pairs of the ortho and meta modes, the lengths of the C−C and C−O forming bonds at the TSs are identical for the ortho pairs: 2.39 and 2.71 Å and the same holds true for the meta ones, being 2.05 and 2.17 Å, respectively; still B3LYP presented lower corresponding bond lengths. The lengths at all TSs indicate that they correspond to asynchronous bond-formation processes, in which the C−C bond formation is more advanced. The longer distance between the C and O atoms indicate that these TSs are associated with a two-center interaction between the α-carbonyl O atom of the ketene and the C atom of the ethylene moiety of the enol ether (vide infra).

Energies. Table 3 shows the B3LYP calculated total and relative energies of all stationary points involved in the DA reactions under study. The activation energies $\Delta E^{\#}$ range from 20.2 kcal/mol for the least favorable **5**/**10** reaction to 5.9 kcal/mol for the most favorable **5**/**11a** one. On the basis of the magnitude of the $\Delta E^{\#}$ and the GEDT values, our DA reactions—with the exception of the **5**/**10** reaction—are classified as polar (P-DA) ones.[33d] In addition, the **5**/**10** reaction indicates that it demands more drastic experimental conditions, in close agreement with its experiment outcomes (it failed at the conditions applied). The fact that no cycloadduct is formed from the reaction of **10** could be attributed to the competitive dimerization reaction of ketene **5**, which is favored in cases of reactions with increased energy requirements.[10] As far as the enol ethers are concerned, the inclusion of an electron releasing O atom, in conjugation with the neighboring ethylene double bond, has a remarkable effect on the activation barriers of the DA between **5** and all enol ethers under study, decreasing the $\Delta E^{\#}$ values to 5.9 kcal/mol. In particular, in the case of the reaction between **5** and dihydropyran **20**, the $\Delta E^{\#}$ value decreases drastically, to almost half of the value (11.5 kcal/mol) of **5**/**10** (20.2 kcal/mol). In addition, the GEDT at its TS found in the former is larger than at the latter, leading thus to a smaller $\Delta E^{\#}$ value. The $\Delta E^{\#}$ value in the dihydrofuran ring decreases further, compared to that of **5**/**20**, as a result of the larger GEDT (0.61 e) at its TS, compared to that (0.51 e) of the latter. The $\Delta E^{\#}$ value of **5**/**19** is of the same order of magnitude as those of the two open chain enol ethers *Z*-**25a**

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Table 4. BP86 Calculated Total[a] (E, au) and Relative Energies (ΔE, kcal/mol) of the Stationary Points Involved in the DA Reactions of 5 with the Enol Ethers, along with GEDT(e) at the Corresponding TSs

dimers		TSs		cycloadducts			
no.	E	no.	E	$\Delta E^{\#}$	GEDT	E	ΔE
5/**10**	−841.2086476	TS**5**/**10**	−841.1805766	17.6	0.25	−841.2530607	−27.9
5/**20**	−877.0716933	TS**5**/**20**	−877.0499375	13.7	0.48	−877.113004	−21.5
5/**19**	−837.9028478	TS**5**/**19**	−837.8835364	12.1	0.55	−837.941184	−24.1
5/*Z*-**25a**	−878.2404846	TS**5**/*Z*-**25a**	−878.2263649	8.9	0.30	−878.2848762	−27.9
5/*E*-**25a**	−878.2378043	TS**5**/*E*-**25a**	−878.2280091	6.1	0.27	−878.2849513	−29.6
5/**11a**	−917.40606824	TS**5**/**11a**	−917.3961801	6.2	0.19	−917.4512867	−28.4

[a]MP2 energies.

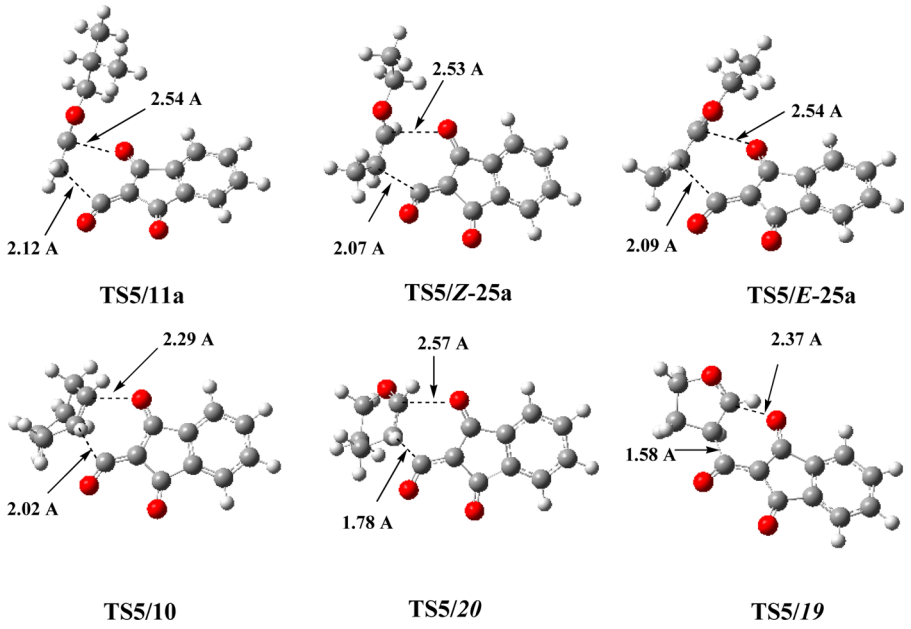


Figure 2. B3LYP calculated geometries of the TSs involved in the DA reactions studied (distances are given in angstroms).

and *E*-**25a**. It should be stressed here that these three enol ethers present almost identical $\Delta E^{\#}$ values, despite the half GEDT (ca. 0.32 e) calculated for the two open chain enol ethers, compared to that of **19**. This should be attributed to their identical ω and N values (vide supra). However, BP86 afforded different $\Delta E^{\#}$ values for the same triad of compounds (see Table 4).

All DA reactions studied are exothermic processes. The corresponding [4 + 2] cycloadducts are located between −18.9 and −24.2 kcal/mol below the reagents. Consequently, the electronic characteristics of the enol ethers and cyclohexene (**10**) have a greater influence over the kinetic parameters (with $\Delta E^{\#}$ values in a 14 kcal/mol range) than over thermodynamic parameters (with ΔE values falling within a 5 kcal/mol range).

A comparison between the B3LYP (Tables 3) and BP86 (Table 4) results shows that (i) the GEDT values of the latter method are slightly smaller than those of the former; (ii) as expected, all BP86 calculated $\Delta E^{\#}$ values are larger than the corresponding B3LYP ones, the only exception being the **5**/**10** reaction; this is due to the lower than the reactants energies of the dimers in the case of the BP86; (iii) the opposite holds true for the relative energy values; (iv) both methods present the same influence of the electronic characteristics of the enol ethers and cyclohexene (**10**) over the kinetic and thermodynamic parameters; and (v) all energy value trends are identical in both methods.

The Geometries of the TSs. The B3LYP calculated geometries of the TSs involved in the DA reactions studied are given in Figure 2. It is clearly seen that all TSs present an asynchronous bond-formation process, the synchronicity broken by the unsymmetric substitution of dienophiles. It is worth noting that, although **10** remains symmetric, it also shows two different forming bonds, differing by only 0.27 Å. It is also seen that the shorter bond length corresponds to the C···C forming bond, of which the former is the nucleophilically activated C of the dienophile, the latter being the ketene electrophilic C atom of its C═O group. BP86 calculated TSs (see Figure S2) show larger corresponding forming bond lengths than those of the B3LYP.

Moreover, the difference between the lenghts of the two σ forming bonds in the reaction, Δd (= b.length1 − b.length2) corresponds to the asynchronicity of the bond formation (see Table 5). TS **5**/**10** shows the lowest Δd of 0.27 Å. The TSs of the two other cyclic enol ethers present the highest Δd values (0.79 Å), in close agreement with the highest polar character of their reactions, verified by their highest GEDT values at the TSs (see Table 2). The TSs of the rest three open chain enol ethers, **11a**, *Z*-**25a**, and *E*-**25a**, show close to each other Δd values (0.42−0.46 Å), located in between the values of the two previous groups of TSs. Based upon the differences in their Δd values, all TSs are asynchronous, verified also by the analysis of the IRC from the TSs to the cycloadducts. This analysis shows

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Table 5. B3LYP Calculated b.length1 (Å) and b.length2 (Å) of the C···C and C···O Forming Bonds, Respectively, along with Their Difference, Δ*d* (Å), at the TSs of the Compounds Studied

TS	b.length1	b.length2	Δ*d*
5/20	1.78	2.57	0.79
5/19	1.58	2.37	0.79
5/*Z*-25a	2.07	2.33	0.46
5/*E*-25a	2.09	2.54	0.45
5/11a	2.12	2.54	0.42
5/10	2.02	2.29	0.27

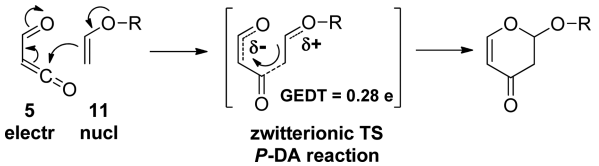
that all cycloadditions under study proceed through a two-stage mechanism.[34] In particular, through a nucleophilic/electrophilic interaction, a C−C bond is formed first. At the second stage of the reaction, the formation of the second C−O bond begins (the former atom is the unreacted C of the enol ether C═C bond, the latter being the α-carbonyl O atom of **5**) initiating the second stage of the reaction. It is worth noting here that the above reaction mechanism is also in accordance with the anaysis of the atomic motions at the unique imaginary frequency, indicating that it is mainly associated with the movement of the C and C atoms along the C−C bond formation, movement of the O and C atoms being negligible. This is also the case with the TSs of all reactions.

The asynchronicities trend, based upon the Δ*d* differences, presented by both BP86 (see also Table S4) and B3LYP methods are identical.

The GEDT Analysis of the TSs and a Possible Mechanism Operating in These Reactions. The natural population analysis allows the evaluation of the GEDT and its direction at the polar DA reactions. In addition, the polar character of the DA reactions was related to the GEDT at the corresponding TS.[35] The natural charges at the TSs are shared between the ketene **5** and the enol ether fragments. The charges of the latter fragments are given in Table 2, showing that in the case of the **5**/**11a** reaction, for instance, the natural atomic charges at the TS were distributed between the **11a** ethylene and the **5** fragments. The net charge at the **11a** ethylene fragment is +0.28 e at TS, that of **5** is −0.28 e, indicating that there is a GEDT taking place from the nucleophile **11a** to the electrophile **5**. All reactions studied showed analogous GEDTs, taking place from the nucleophiles to the electrophile **5**, ranging from 0.26 (**10**) to 0.61 (**19**).

In Scheme 16, a possible schematic representation of the **5**/**11a** P-DA reaction is given. The electron movement

Scheme 16. A Possible Schematic Representation of the 5/11a P-DA Reaction



throughout the cycloaddition is shown with arrows. In particular, the arrows plotted show the GEDTs along the first part of the reaction. It should be stressed out here that (i) the TS is zwitterionic in nature, and (ii) due to the two-stage mechanism of the reaction, after the first C−C bond formation, there is a back-donation process during the ring closure.

The correlation between the $\Delta E^{\#}$ and the GEDT values at the TS, relating the acceleration of the DA reactions with the increase in the polar character, was examined next. Due to the different nature of the reactants used in this study, two linear correlations were attempted: one involving the three cyclic derivatives, **10**, **19**, and **20** and the second referring to the three open chain ones, **11a**, *Z*-**25a**, and *E*-**25a**. The former afforded an almost excellent linear correlation (R^2 = 0.9997). This result supports the observation that an increase in the polar character of the cycloaddition is accompanied by an acceleration of the DA reactions. However, the worst linear correlation found (R^2 = 0.8929) for the open chain derivatives is in line with the discrepancy observed between their $\Delta E^{\#}$ and *N* index values, meaning possibly that they do not constitute a group of analogous compounds. BP86 showed worse corresponding R^2 values (0.9962 and 0.4737, respectively) than those of the B3LYP.

Based on the structures of the initial cycloadducts, derived theoretically, a reasonable explanation of the ease with which they are transformed to their open-ring tautomers is attempted herein. This assessment could be based upon the dihedral angle value formed by the planes defined by the O1−C2−C3 and C2−C3−H atoms of the pyranone ring, as this ring-opening reaction may be considered equivalent to an elimination reaction (cleavage of the O1−C2 and C3−H bonds resulting to the formation of the C2═C3 double bond). Based on this consideration, the reaction is expected to be favorable in cases where this dihedral angle approximates 180° and the bonds possess anti-coplanar arrangement. For products **12a**, **21**, **24**, *cis*-**26a**, and *trans*-**26a** these dihedral angles have been calculated (BP86) to be 173.4°, 162.2°, 66.5°, 59.6°, and 168.45°, respectively. A second important factor that might affect the ease of the pyranone ring opening is the relative stability of the tautomerized products, which is related to steric factors. In particular, products in which the stereochemistry of the newly formed C═C double bond is *Z* are expected to have increased energy content than the corresponding with the *E* stereochemistry, due to the developing crowding as already have been mentioned. These two factors (angle 162.2°, *E*-configuration of the C2═C3 bond) met in the case of product **21**, wherein the ring-opening reaction is predicted to be particularly favorable, a fact being in very good agreement with the experimental results (see Table 1, entries 10 and 11). In cases where the dihedral angle differs much from the ideal value, but the ring-opening results in a product with *E*-configuration of the double bond, the transforming molecule can adopt the right conformation, consuming the required energy, so the critical linkages O1−C2 and C3−H can acquire anti-coplanar arrangement. This is the case with the ring-opening of product **24**, where rather relatively higher temperatures are required (Table 1, entries 13 and 14). In case of cycloadduct **12a**, despite the ideal value of the dihedral angle, the reaction requires relatively higher temperatures because the detachment of the hydrogen atom, located in the ideal position, would lead to the less stable *Z*-isomer product. With consumption of energy, the configuration of **12a** can be reversed, and the second hydrogen atom on the C3—the abstraction of which will result to the *E*-product—can be found in the correct anti-coplanar arrangement (Table 1, entries 1 and 2). Regarding the tautomerization of **26a**, the value of dihedral angle in the *trans*-**26a** is indeed suitable (168.45°), but the abstraction of the 3-H would lead to the less stable *Z*-product. Due to the absence of a second 3-H, which in another less

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

stable conformation could be found in the proper position for abstraction, the formation of the more stable *E*-**27a** product is not feasible. Thereby, the ring opening of the *trans*-**26a** proceeds only through conversion to the *cis*-**26a** isomer (Scheme 14). The C3−H bond of *cis*-**26a** can receive the anti-coplanar arrangement with the C2−O bond and lead to the more stable *E*-**27a** product by inversion of the conformation of the pyranone ring.

The dihedral angle values φ between the C−C−H_a and C−C−H_b planes for the optimized gas-phase geometries of the *cis*-**26a** and *trans*-**26a** have been calculated 53.2° and 78.4°, respectively, and indicate the cis-configuration for the isomer with the larger value of coupling constant, if it is of course assumed that the same conformers exist both in gas-phase and in solution. Therefore, it could be probably concluded that the isomer **26a** with $J_{a,b}$ = 5.8 Hz has the proper cis-configuration both for EtOH abstraction and opening of the pyranone ring.

CONCLUSIONS

In conclusion, indanedioneketene (**5**), produced in situ during the thermal decomposition of phenyliodonium ylide of lawsone (**4**), participates in inverse electron demand [4 + 2] cycloaddition reactions with electron-rich alkenes, such as enol ethers, acting as the 4π-participant. The cycloadditions present a total ortho regioselectivity and have a large polar character based upon the calculated ω and N indexes, the magnitude of the $\Delta E^{\#}$, and the GEDT values at the TSs. A nonconcerted two-stage one-step mechanism was also found to operate, and the flux of electron density takes place from the nucleophilic enol ethers to the electrophilic ketene **5**. In these asynchronous processes, the C−C σ-bond is first formed by coupling of the two centers located at the most electrophilic carbon of ketene **5** and the most nucleophilic center of the dienophile.

The formation as well as the isolation of the cycloadducts 2,3-dihydroindeno[1,2-*b*]pyran-4,5-diones **12**, **21**, **23**, **26**, **33**, and **37** is directly dependent on the temperature and duration of the thermal reaction. Relatively elevated temperatures (above 40−45 °C) are required (higher than the degradation temperature of ylide **4**) for an effective cycloaddition reaction, but prolonged heating results in isomerization of the initial cycloadducts to the 2-alkoxyallylidene-indenedione derivatives **13**, **22**, **24**, **27**, **35**, **32**, and **38** through dihydropyranone ring opening. Beyond their thermal instability, the initial cycloadducts are also sensitive in acidic environment, apparently due to their acetalic structure, transforming to hydroxyallylidene-indenediones **15** or through elimination of alcohol to indenopyranediones **29**, a condition that precludes their isolation by column chromatography.

Besides the interest around the chemical behavior of indanedioneketene, one of the few known α,α'-dioxoketenes, the resulting indenopyrandiones, and particularly the alkoxyallylidene-indenediones have interesting structures and are promising candidates for biological applications.[36,37] The biological properties of the compounds prepared in this study are under investigation.

EXPERIMENTAL SECTION

General. All vinyl ethers were commercially available. Melting points were determined on a capillary melting point apparatus and are uncorrected. IR spectra were recorded on a FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a 300 or 500 MHz spectrometer in $CDCl_3$ unless otherwise specified and quoted relative to tetramethylsilane as internal reference. Mass spectral data were obtained on a high-performance liquid chromatograph/mass spectrometer (LC-MS) equipped with ESI interface. Due to the instability of products **12**, **21**, **23**, **26**, and **33**, their mass spectra were exceptionally obtained by direct injection in the mass spectrometer. The reactions under MW irradiation were performed in closed vessels in a Biotage Initiator 2.0 with external sensor for measuring reaction mixture temperatures. Column chromatography was performed on silica gel (70−230 mesh), and analytical TLC was carried out on precoated silica gel plates (F_{254}, 0.25 mm). Petroleum ether (PE) refers to the fraction 40−60 °C.

General Procedure for the Reaction of Phenyliodonium Ylide 4 with Vinyl Ethers. *Thermal Reaction (Method I).* A suspension of 2-oxido-3-phenyliodonio-1,4-naphthoquinone (**4**)[38] (1 mmol) in excess of the appropriate vinyl ether was stirred under reflux until a clear solution was formed (from 15 min to 7 h) indicating the decomposition of **4**. In some cases CH_2Cl_2 was used as solvent. The excess of vinyl ether (and CH_2Cl_2) was removed under reduced pressure, and petroleum ether was added. The mixture was concentrated again in order to remove as much of the iodobenzene byproduct was possible, and its composition was estimated by ^{1}H NMR. The residue was treated with CH_2Cl_2/PE or Et_2O/PE to achieve the successive crystallization or sometimes co-crystallization of the corresponding alkoxyallylidene-indenediones **12**, **21**, **23**, **26**, **33** and hydroxyallylidene-indenedione **15**. All solid products were isolated by filtration and recrystallized with CH_2Cl_2/PE. The filtrate was concentrated and subjected to column chromatography on silica gel. The column was eluted with petroleum ether containing increasing amounts of ethyl acetate (from 15% to 100%) as eluent to afford the esters **14**, **28**, and the allylidene-indenedione derivatives **13**, **22**, **24**, **27**, **32**, in order of elution. In the case of (cyclohex-1-en-1-yloxy)(trimethyl)silane, 6,7,8,9-tetrahydroindeno[1,2-*b*]chromene-10,11-dione (**31**) was also eluted from the column.

Reaction under MW Irradiation (Method II). A mixture of 2-oxido-3-phenyliodonio-1,4-naphthoquinone (**4**) with the appropriate vinyl ether and CH_2Cl_2 was irradiated in a closed vessel at a certain temperature and for a determined period of time as specified in each case. Three reaction protocols were applied:

- Protocol A. Reactants: Ylide **4** (1 mmol), vinyl ether (0.5 mL), CH_2Cl_2 (2 mL). Irradiation at 70 °C for 30 min.
- Protocol B. Reactants: Ylide **4** (0.5 mmol), vinyl ether (0.3 mL), CH_2Cl_2 (1 mL). Irradiation at 100 °C for 3 min.
- Protocol C. Reactants: Ylide **4** (0.5 mmol), vinyl ether (0.3 mL), CH_2Cl_2 (1 mL). Irradiation at 140 °C for 20 min.

The reaction mixture was then concentrated at reduced pressure, and petroleum ether was added. The mixture was concentrated again to remove the larger amount of iodobenzene byproduct, and its composition was estimated by ^{1}H NMR. The estimated yields of the corresponding products are recorded in Table 1. The residue was treated with CH_2Cl_2/PE or Et_2O/PE to achieve the crystallization of the relevant product(s) in each case. The solid products were isolated by filtration. Isolation of the respective products, which could not be crystallized, was done by column chromatography (petroleum ether containing increasing amounts of ethyl acetate from 15% to 100% as eluent) of the residue.

Reaction of Ylide 4 with 2-Methyl-1-(vinyloxy)propane (11a). Method I. A suspension of ylide **4** (376 mg, 1 mmol) in 2-methyl-1-(vinyloxy)propane (2 mL) was stirred under reflux for 1.5 h. Product **12a** (144 mg, 54%) was precipitated upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE. Column chromatography of the residue afforded compounds **14a** (69 mg, 20%) and **13a** (36 mg, 13%) in order of elution.

Method II. Protocol A: Compound **12a** (204 mg, 75%) was precipitated upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE.

Protocol B: After work up, the composition of the concentrated reaction mixture was estimated by ^{1}H NMR and the yields are recorded in Table 1.

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Protocol C: Compound **13a** (48 mg, 35%) was crystallized upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE. The residue was subjected to column chromatography to afford **14a** (42 mg, 24%) and **13a** (41 mg, 30%).

*2-Isobutoxy-2,3-dihydroindeno[1,2-b]pyran-4,5-dione (**12a**).* Yellow solid; mp 162−166 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1719, 1663, 1612, 1114, 1011; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71−7.63 (m, 1H), 7.60−7.49 (m, 3H), 5.91 (dd appearing as broad s, 1H), 3.78 (dd, J_1 = 9.3 Hz, J_2 = 6.5 Hz, 1H), 3.52 (dd, J_1 = 9.3 Hz, J_2 = 6.8 Hz, 1H), 2.87 (dd, J_1 = 16.7 Hz, J_2 = 3.9 Hz, 1H), 2.82 (dd, J_1 = 16.7 Hz, J_2 = 4.7 Hz, 1H), 2.00−1.86 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.3, 184.8, 182.9, 135.1, 134.0, 133.9, 133.1, 123.0, 121.2, 107.9, 106.8, 77.6, 42.6, 28.3, 19.0; ESI positive 295 $(M + Na)^+$; Anal. calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.80; H, 5.65.

*2-(1-Hydroxy-3-isobutoxyallylidene)-1H-indene-1,3(2H)-dione (**13a**).* Yellow solid; mp 90−92 °C (CH_2Cl_2/ PE); IR (KBr) cm^{-1} 3446, 1698, 1643, 1608, 1245, 1095; ^1H NMR (300 MHz, $CDCl_3$): δ = 13.27 (br, 1H), 7.97 (d, J = 12.4 Hz, 1H), 7.83−7.77 (m, 2H), 7.72−7.63 (m, 2H), 6.75 (d, J = 12.4 Hz, 1H), 3.85 (d, J = 6.9 Hz, 2H), 2.18−2.03 (m, 1H), 1.00 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 189.5, 176.1, 164.6, 140.7, 138.5, 134.4, 133.6, 122.2, 121.9, 105.2, 97.3, 78.3, 28.1, 18.9; ESI positive 273 $(M + H)^+$, 295 $(M + Na)^+$; Anal. calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.79; H, 5.67.

*Isobutyl 2-(1-isobutoxyethyl)-1,3-dioxo-2,3-dihydro-1H-indene-2-carboxylate (**14a**).* Yellow oil; IR (KBr) cm^{-1} 1760, 1713, 1597, 1256, 1087; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06−7.96 (m, 2H), 7.86−7.79 (m, 2H), 4.42 (q, J = 6.4 Hz, 1H), 3.92 (dd, J_1 = 10.2 Hz, J_2 = 6.4 Hz, 1H), 3.83 (dd, J_1 = 10.2 Hz, J_2 = 6.5 Hz, 1H), 3.24 (dd, J_1 = 8.7 Hz, J_2 = 5.9 Hz, 1H), 2.83 (dd, J_1 = 8.7 Hz, J_2 = 5.9 Hz, 1H), 1.87−1.73 (m, 2H), 1.52 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.9 Hz, 6H), 0.53 (d, J = 6.8 Hz, 3H), 0.47 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 164.9, 143.7, 142.9, 135.5, 135.4, 123.43, 123.37, 77.8, 76.3, 71.7, 68.9, 28.3, 27.6, 18.9, 18.7, 14.5; ESI positive 369 $(M + Na)^+$; Anal. calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.12; H, 7.70.

*Reaction of Ylide **4** with 1-(Vinyloxy)butane (**11b**). Method I.* A suspension of ylide **4** (376 mg, 1 mmol) in 1-(vinyloxy)butane (1 mL) was stirred under reflux for 35 min. Product **12b** (155 mg, 57%) was precipitated upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE. Column chromatography of the residue afforded compounds **14b** (14 mg, 4%) and **13b** (81 mg, 30%) in order of elution.

Method II. Protocol A: Compound **12b** (200 mg, 74%) was crystallized. Compounds **14b** (32 mg, 9%) and **13b** (25 mg, 9%) were eluted from the chromatography column.

Protocol B: After work up, the composition of the concentrated reaction mixture was estimated by ^1H NMR, and the yields are recorded in Table 1.

Protocol C: Compound **13b** (50 mg, 37%) was crystallized upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE and isolated by filtration. The filtrate was concentrated and subjected to column chromatography to afford an additional portion of **13b** (45 mg, 33%).

*2-Butoxy-2,3-dihydroindeno[1,2-b]pyran-4,5-dione (**12b**).* Yellow solid; mp 176−177 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1715, 1648, 1609, 1216, 1094; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71−7.62 (m, 1H), 7.60−7.46 (m, 3H), 5.92 (dd appearing as broad s, 1H), 4.01 (dt appearing as dd, J_1 = 9.5 Hz, J_2 = 6.6 Hz, 1H), 3.79 (dt appearing as dd, J_1 = 9.5 Hz, J_2 = 5.9 Hz, 1H), 2.91 (dd, J_1 = 16.9 Hz, J_2 = 3.7 Hz, 1H), 2.80 (dd, J_1 = 16.9 Hz, J_2 = 4.4 Hz, 1H), 1.68−1.57 (m, 2H), 1.43−1.29 (m, 2H), 0.90 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.3, 184.8, 182.9, 135.0, 134.1, 133.8, 133.1, 122.9, 121.2, 107.9, 106.8, 70.8, 42.6, 31.3, 18.9, 13.6; ESI positive 295 $(M + Na)^+$; Anal. calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.82; H, 6.12.

*2-(3-Butoxy-1-hydroxyprop-2-en-1-ylidene)-1H-indene-1,3(2H)-dione (**13b**).* Yellow solid; mp 84−87 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1695, 1644, 1602, 1247, 1094; ^1H NMR (300 MHz, $CDCl_3$): δ = 13.45 (br, 1H), 7.96 (d, J = 12.9 Hz, 1H), 7.82−7.76 (m, 2H), 7.70−7.60 (m, 2H), 6.75 (d, J = 12.9 Hz, 1H), 4.08 (t, J = 6.5 Hz, 2H), 1.77 (quin, J = 7.5 Hz, 2H), 1.47 (sex, J = 7.5 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 189.1, 176.1, 164.5, 140.7, 138.5, 134.4, 133.6, 122.2, 121.9, 105.2, 97.3, 71.9, 30.8, 19.0, 13.7; ESI negative 271 $(M - H)^+$; Anal. calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.69; H, 5.66.

*Butyl 2-(1-Butoxyethyl)-1,3-dioxoindane-2-carboxylate (**14b**).* Oil; IR (KBr) cm^{-1} 1760, 1715, 1595, 1257, 1093; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.07−7.98 (m, 2H), 7.89−7.82 (m, 2H), 4.44 (q, J = 6.3 Hz, 1H), 4.16−4.03 (m, 2H), 3.46 (dt, J_1 = 9.0 Hz, J_2 = 6.0 Hz, 1H), 3.12 (dt, J_1 = 14.1 Hz, J_2 = 6.6 Hz, 1H), 1.52 (d, J = 6.3 Hz, 3H), 1.29−1.14 (m, 4H), 0.99−0.87 (m, 4H), 0.84 (t, J = 7.4 Hz, 3H), 0.67 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 165.0, 143.7, 142.8, 135.5, 135.4, 123.5, 123.4, 77.7, 69.3, 69.0, 65.8, 31.4, 30.3, 18.8, 14.7, 13.5; ESI positive 369 $(M + Na)^+$; Anal. calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.56. Found: C, 69.59; H, 7.75.

*Reaction of Ylide **4** with Ethoxyethene (**11c**). Method I.* A mixture of ylide **4** (376 mg, 1 mmol) and ethoxyethene (1 mL) in CH_2Cl_2 (10 mL) was refluxed for 8 h. The unreacted ylide **4** (132 mg, 35%) was separated from the reaction mixture by filtration. The filtrate was concentrated under reduced pressure, and petroleum ether was added. The mixture was concentrated again in order to remove more of the iodobenzene, and then it was treated with petroleum ether. Product **15a** (41 mg, 19%) was crystallized and isolated by filtration. The filtrate was concentrated and subjected to column chromatography to afford product **14c** (76 mg, 9%) and indanedione (**8**, 47 mg, 32%).

Method II. Protocol A: Careful concentration of the reaction mixture under reduced pressure afforded compound **12c** almost quantitatively, as estimated by ^1H NMR. Upon treatment of the oily product with CH_2Cl_2/PE, crystals of **12c** (105 mg, 43%) were precipitated and collected by filtration. An attempt to receive the remaining quantity of **12c** by treating the concentrated filtrate with CH_2Cl_2/PE resulted in its transformation to **15a**.

Protocol B: Compound **12c** (50 mg, 40%) was crystallized upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE.

Protocol C: Compound **13c** (66 mg, 54%) was crystallized upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE. Column chromatography afforded compound **14c** (35 mg, 24%).

*2-Ethoxy-2,3-dihydroindeno[1,2-b]pyran-4,5-dione (**12c**).* Yellow solid; mp 89−92 °C (dec) (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1718, 1650, 1615, 1170; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65−7.58 (m, 1H), 7.57−7.48 (m, 3H), 5.94 (dd appearing as t, J = 4.5 Hz, 1H), 4.18−4.00 (m, 1H), 3.86−3.78 (m, 1H), 2.93 (dd, J_1 = 17.0 Hz, J_2 = 3.8 Hz, 1H), 2.79 (dd, J_1 = 17.0 Hz, J_2 = 4.5 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.0, 184.5, 182.7, 134.7, 133.7, 133.5, 132.9, 122.4, 121.0, 107.5, 106.4, 66.4, 42.4, 14.7. ESI positive 245 $(M + H)^+$; Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 69.03; H, 5.10.

*(E)-2-(3-Ethoxy-1-hydroxyallylidene)-1H-indene-1,3(2H)-dione (**13c**).* Yellow solid; mp 84−87 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1697, 1644, 1605, 1246, 1096; ^1H NMR (300 MHz, $CDCl_3$): δ = 13.27 (brs, 1H), 7.93 (d, J = 12.6 Hz, 1H), 7.81−7.73 (m, 2H), 7.69−7.59 (m, 2H), 6.75 (d, J = 12.6 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 188.9, 176.0, 164.1, 140.8, 138.7, 134.4, 133.5, 122.3, 121.9, 105.3, 97.6, 67.8, 14.4; ESI positive 245 $(M + H)^+$; Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.70; H, 4.85.

*Ethyl 2-(1-ethoxyethyl)-1,3-dioxoindane-2-carboxylate (**14c**).* Oil; IR (KBr) cm^{-1} 1758, 1712, 1618, 1242, 1092; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.06−7.97 (m, 2H), 7.89−7.81 (m, 2H), 4.46 (q, J = 6.4 Hz, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.55−3.42 (m, 1H), 3.27−3.15 (m, 1H), 1.51 (d, J = 6.4 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.5, 165.0, 143.7, 142.8, 135.5, 123.7, 123.5, 69.0, 65.3, 62.1, 14.9, 14.8, 13.9; ESI positive 313 $(M + Na)^+$; Anal. calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.12; H, 6.15.

*Reaction of Ylide **4** with 2,3-Dihydrofuran (**19**). Method I.* A suspension of ylide **4** (376 mg, 1 mmol) in 2,3-dihydrofuran (2 mL) was stirred under reflux for 7 h, and then the reaction mixture was

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

subjected to the work up described in general procedure. Product **21** (90 mg, 37%) was crystallized and isolated by filtration. Column chromatography of the residue afforded compound **22** (53 mg, 22%).

Method II. Protocol A: The unreacted ylide **4** (60 mg, 16%) was separated from the reaction mixture by filtration. The filtrate was concentrated at reduced pressure, petroleum ether was added and the mixture was concentrated again to remove as much iodobenzene byproduct as possible. Products **21** and **22** were detected in the residue, in yields estimated by ^{1}H NMR and recorded in Table 1.

Protocol B: The reaction mixture was treated as described in general procedure. Products **21** and **22** were detected in the residue, in yields estimated by ^{1}H NMR and recorded in Table 1.

Protocol C: After work up, product **22** (82 mg, 68%) was crystallized and collected by filtration. An additional quantity of **22** (24 mg, 20%) was isolated by column chromatography of the residue.

*2,3,3a,10a-Tetrahydrofuro[2,3-b]indeno[2,1-e]pyran-4,5-dione (**21**).* Yellow solid; mp 168−170 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1727, 1711, 1677, 1655, 1235, 1141; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76−7.66 (m, 1H), 7.63−7.55 (m, 3H), 6.32 (d, J = 3.9 Hz, 1H), 4.51−4.32 (m, 1H), 4.28−4.12 (m, 1H), 3.21−3.05 (m, 1H), 2.62−2.51 (m, 1H), 2.28−2.08 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.4, 184.8, 184.6, 134.7, 134.4, 134.3, 133.3, 123.0, 121.9, 110.5, 104.5, 69.9, 51.0, 28.0; ESI positive 265 (M + Na)$^+$; Anal. calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.48; H, 4.06.

*2-[4,5-Dihydrofuran-3-yl(hydroxy)methylene]-1H-indene-1,3(2H)-dione (**22**).* Yellow solid; mp 99−103 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 3437, 1685, 1633, 1612, 1156; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 15.00 (brs, 1H), 9.33 (s, 1H), 7.76−7.69 (m, 2H), 7.66−7.58 (m, 2H), 4.68 (t, J = 9.7 Hz, 2H), 3.06 (t, J = 9.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.0, 188.1, 175.4, 166.6, 139.7, 137.4, 134.3, 133.3, 122.1, 121.7, 113.0, 105.4, 73.4, 27.5; ESI-HRMS m/z calcd for $C_{14}H_{10}O_4$ + Na (MNa$^+$) 265.04713, found 265.04743.

*Reaction of Ylide **4** with 3,4-Dihydro-2H-pyran (**20**). Method I.* A suspension of ylide **4** (376 mg, 1 mmol) in 3,4-dihydro-2*H*-pyran (1 mL) was stirred under reflux for 15 min. Upon treatment of the concentrated reaction mixture with petroleum ether, an inseparable mixture of compounds **23** and **24** precipitated, in yields 57% and 42%, respectively, as indicated by ^{1}H NMR. Column chromatography of this mixture afforded pure product **24** (100 mg, 35%).

Method II. Protocol A: The unreacted ylide **4** (19 mg, 5%) was separated from the reaction mixture by filtration. The filtrate was concentrated at reduced pressure, petroleum ether was added, and the mixture was concentrated again to remove as much iodobenzene byproduct as possible. Products **23** and **24** were detected in the residue, in yields estimated by ^{1}H NMR and recorded in Table 1.

Protocol B: The reaction mixture was treated as described previously (protocol A). Products **23** and **24** were detected in the residue, in yields estimated by ^{1}H NMR and recorded in Table 1.

Protocol C: After work up, product **24** (57 mg, 44%) was crystallized upon treatment of the concentrated reaction mixture with CH_2Cl_2/Et_2O/PE and collected by filtration. An additional quantity of **24** was isolated by column chromatography of the residue (46 mg, 36%).

*Data for 3,4,4a,11a-Tetrahydro-2H-indeno[1,2-b]pyrano[3,2-e]-pyran-5,6-dione (**23**).* ^{1}H NMR and ^{13}C NMR spectra of **23**, as they result by subtraction of the corresponding peaks for compound **24** from the spectra of their mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80−7.55 (m, 4H), 6.00 (3.3 Hz, 1H), 4.15−3.96 (m, 2H), 2.78−2.66 (m, 1H), 2.05−1.99 (m, 1H), 1.90−1.74 (m, 3H); ^{13} C NMR (75 MHz, $CDCl_3$): δ = 187.5, 185.9, 134.7, 134.3, 134.1, 133.3, 123.0, 121.7, 106.4, 104.8, 104.6, 63.4, 46.8, 23.1, 22.2.

*2-[3,4-Dihydro-2H-pyran-5-yl(hydroxy)methylene]-1H-indene-1,3(2H)-dione (**24**).* Yellow solid; mp 116−119 °C (CH_2Cl_2/PE) ;IR (KBr) cm^{-1} 3447, 1686, 1640, 1616, 1232, 1181; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 15.68 (brs, 1H), 9.08 (s, 1H), 7.74−7.67 (m, 2H), 7.64−7.57 (m, 2H), 4.22 (t, J = 5.3 Hz, 2H), 2.45 (t, J = 6.3 Hz, 2H), 1.98 (tt, appearing as quin, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.7, 187.6, 181.8, 163.2, 139.3, 137.2, 134.2, 133.3, 122.2, 121.5, 109.4, 104.8, 67.5, 21.0, 18.7; ESI-HRMS m/z calcd for $C_{15}H_{12}O_4$ + Na (MNa$^+$) 279.06278, found 279.06284.

*Reaction of Ylide **4** with 1-Ethoxyprop-1-ene (**25a**). Method I.* A suspension of ylide **4** in 1-ethoxyprop-1-ene (E:Z = 1:2) (2 mL) was stirred under reflux for 4 h. A mixture of *cis*/*trans*-**26a** (77 mg, 30%) was crystallized upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE. The filtrate was concentrated and subjected to column chromatography to afford products **28a** (15 mg, 5%) and **27a** (16 mg, 12%) in order of elution.

The reaction was repeated, and after concentration of the excess of 1-ethoxyprop-1-ene, CH_2Cl_2 (2 mL) and CF_3COOH (3 drops) was added, and the mixture was refluxed for 4h. Treatment of the concentrated reaction mixture with petroleum ether resulted to the precipitation of compound **29a** (180 mg, 85%).

Method II. Protocol A: After work up, pure *cis*-**26a** stereoisomer (60 mg, 23%) was obtained by crystallization with Et_2O/PE.

Protocol B: After work up, the composition of the concentrated reaction mixture was estimated by ^{1}H NMR, and the yields are recorded in Table 1.

Protocol C: Compound **27a** (26 mg, 20%) was crystallized upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE. Column chromatography of the residue afforded product **28a** (18 mg, 12%) and an additional portion of **27a** (51 mg, 40%).

*2-Ethoxy-3-methyl-2,3-dihydroindeno[1,2-b]pyran-4,5-dione (**26a**).* (Mixture of *trans*:*cis* diastereoisomers, ratio 0.68:1), yellow solid; IR (KBr) cm^{-1} 1720, 1655, 1609, 1546, 1184; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69−7.60 (m, 1.68 H), 7.58−7.43 (m, 5H), 5.77 (d, J = 3.3 Hz, 0.68 H), 5.53 (d, J = 5.8 Hz, 1 H), 4.15−3.93 (m, 1.68 H), 3.89−3.71 (m, 1.68 H), 2.94−2.83 (m, 0.68 H), 2.80−2.68 (m, 1 H), 1.38−1.20 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.5, 186.7, 186.2, 184.2, 184.0, 135.3, 135.1, 134.2, 134.1, 133.9, 133.8, 133.0, 132.9, 122.9, 122.9, 121.1, 120.9, 111.2, 109.4, 107.7, 106.9, 66.9, 66.8, 46.2, 45.4, 15.0, 14.9, 12.0, 8.8; ESI positive 281 (M + Na)$^+$; Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 70.02; H, 5.61.

(2S,3S*)-2-Ethoxy-3-methyl-2,3-dihydroindeno[1,2-b]pyran-4,5-dione (**26a**).* Yellow solid; mp 156−159 °C (Et_2O/PE); IR (KBr) cm^{-1} 1725, 1642, 1625, 1167; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.70−7.64 (m, 1H), 7.61−7.49 (m, 3H), 5.53 (d, J = 5.8 Hz, 1H), 4.18−4.07 (m, 1H), 3.90−3.79 (m, 1H), 2.81−2.70 (m, 1H), 1.30 (two overlapping t, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.4, 186.5, 184.0, 135.2, 134.3, 133.9, 132.9, 122.9, 121.1, 111.2, 109.3, 106.9, 46.2, 14.9, 11.9; ESI positive 281 (M + Na)$^+$; Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.49; H, 5.27.

*(E)-2-(3-Ethoxy-1-hydroxy-2-methylallylidene)-1H-indene-1,3(2H)-dione (**27a**).* Yellow solid; mp 99−102 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1681, 1624, 1212; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 15.83 (brs, 1H), 9.10 (s, 1H), 7.77−7.67 (m, 2H), 7.67−7.55 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.87 (s, 3 H), 1.46 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.7, 188.0, 183.9, 166.4, 139.4, 137.3, 134.2, 133.3, 122.1, 121.6, 110.2, 104.8, 71.2, 15.5, 8.5; ESI positive 313 (M + Na + MeOH)$^+$; Anal. calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 70.00; H, 5.61.

*Ethyl 2-(1-ethoxypropyl)-1,3-dioxo-2,3-dihydro-1H-indene-2-carboxylate (**28a**).* Yellow oil; IR (KBr) cm^{-1} 1752, 1712, 1596, 1253; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04−7.99 (m, 2H), 7.85−7.82 (m, 2H), 4.25 (dd, J_1 = 9.0 Hz, J_2 = 3.3 Hz, 1H), 4.14 (dq, J_1 = 14.1 Hz, J_2 = 7.5 Hz, 1H) overlapping with a peak at 4.13 (dq, J_1 = 14.1 Hz, J_2 = 7.5 Hz, 1H), 3.53 (dq, J_1 = 14.1 Hz, J_2 = 7.4 Hz, 1H), 3.34 (dq, J_1 = 14.1 Hz, J_2 = 7.4 Hz, 1H), 1.98−1.83 (m, 2H), 1.15 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.4 Hz, 3H), 0.79 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.4, 195.2, 165.2, 143.9, 142.9, 135.6, 135.5, 123.7, 123.4, 84.4, 69.6, 69.2, 62.1, 25.4, 15.2, 13.9, 11.5; ESI positive 327 (M + Na)$^+$; Anal. calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.89; H, 6.58.

*3-Methylindeno[1,2-b]pyran-4,5-dione (**29a**).* Pale-brown solid; mp 146−149 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1724, 1641, 1268, 1162; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81 (s, 1H), 7.66−7.61 (m, 1H), 7.58−7.49 (m, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.5, 178.8, 172.9, 149.6, 134.2, 133.9, 132.1, 131.8, 130.0, 123.3, 120.6, 113.4, 10.7; ESI positive 235 (M + Na)$^+$; Anal. calcd for $C_{13}H_8O_3$: C, 73.58; H, 3.80. Found: C, 73.33; H, 3.87.

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

*Reaction of Ylide **4** with 1-Ethoxybut-1-ene (**25b**). Method I.* A suspension of ylide **4** (376 mg, 1 mmol) in 1-ethoxybut-1-ene (*E*:*Z* = 1:1.45) (4 mL) was stirred under reflux. The reaction mixture became clear after 25 min and then was concentrated in vacuum. After the previously described in general procedure work up, product **26b** was detected in the crude reaction mixture by ^{1}H NMR spectroscopy, but its crystallization from the reaction mixture (treatment with CH_2Cl_2/PE) failed. Column chromatography of the reaction mixture afforded products **28b** (32 mg, 12%) and **27b** (33 mg, 12%) in order of elution.

The reaction was repeated, and after concentration of the excess of 1-ethoxybut-1-ene, CH_2Cl_2 (2 mL) and CF_3COOH (3 drops) were added, and the mixture was gently heated for 4 h. Compound **29b** (135 mg, 60%) was obtained after column chromatography of the concentrated reaction mixture (silica gel, petroleum ether/ethyl acetate 3:1).

Method II. Protocol A: The composition of the concentrated reaction mixture was estimated by ^{1}H NMR, and the yields are recorded in Table 1. The isolation of the initial cycloadduct **26b**, although detectable by ^{1}H NMR, was unsuccessful.

Protocol B: The isolation of the initial cycloadduct **26b**, although detectable by ^{1}H NMR, was unsuccessful. Upon treating the reaction mixture with a few drops of CH_2Cl_2, product **15b** (22 mg, 18%) was crystallized and collected by filtration.

Protocol C:The crystallization of product **27b** upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE or Et_2O/PE was unsuccessful. Products **28b** and **27b** were separated by column chromatography. Due to their approximately equal R_f, repeated columns (silica gel, petroleum ether/ethyl acetate 5:1) were necessary for their purification. Finally, 37 mg (23%) of **28b** and 54 mg (40%) of **27b** were collected. The oily fraction **27b** was crystallized by treatment with CH_2Cl_2/PE.

*(E)-2-(2-(Ethoxymethylene)-1-hydroxybutylidene)-1H-indene-1,3(2H)-dione (**27b**).* Yellow solid; mp 99−103 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 1687, 1625, 1222; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.01 (s, 1H), 7.75−7.71 (m, 2H), 7.66−7.59 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 2.43 (q, J = 7.4 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.8, 188.1, 183.9, 166.2, 139.3, 137.2, 134.2, 133.3, 122.1, 121.6, 116.4, 104.9, 71.3, 16.8, 15.6, 13.4; ESI negative 271 (M-H)$^+$; Anal. calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.80; H, 5.67.

*Ethyl 2-(1-Ethoxybutyl)-1,3-dioxo-2,3-dihydro-1H-indene-2-carboxylate (**28b**).* Yellow oil; IR (KBr) cm^{-1} 1758, 1713, 1596, 1253, 1083; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.06−8.00 (m, 2H), 7.87−7.83 (m, 2H), 4.33 (dd, J_1 = 9.5 Hz, J_2 = 2.8 Hz, 1H), 4.153 (dq appearing as q, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 1H) overlapping with a peak at 4.153 (dq appearing as q, J_1 = 14.1 Hz, J_2 = 7.1 Hz, 1H) 3.52 (dq, J_1 = 14.0 Hz, J_2 = 7.1 Hz, 1H), 3.27 (dq, J_1 = 14.0 Hz, J_2 = 7.1 Hz, 1H), 1.93−1.78 (m, 2H), 1.58−1.50 (m, 2H), 1.56 (t, J = 7.1 Hz, 3H), 0.97 (t, J = 7.3 Hz, 3H), 0.77 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.5, 195.3, 165.1, 143.8, 143.7, 135.7, 135.5, 123.7, 123.4, 82.7, 69.4, 69.2, 62.1, 34.4, 20.2, 15.2, 14,1, 13.9; ESI positive 341 (M + Na)$^+$; Anal. calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.19; H, 7.14.

*3-Ethylindeno[1,2-b]pyran-4,5-dione (**29b**).* Pale-brown solid; mp 156−160 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 3428, 1711, 1640, 1212, 1163; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75−7.63 (m, 2H), 7.58−7.43 (m, 3H), 2.49 (q, J = 7.5 Hz, 2H), 1.18 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.7, 178.8, 172.8, 149.6, 135.6, 134.6, 133.8, 133.3, 132.3, 123.7, 120.7, 114.1, 18.9, 12.4; ESI positive 227 (M + H)$^+$, 249 (M + Na)$^+$; Anal. calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.58; H, 4.31.

*2-[(1,3-Dioxo-1H-inden-2(3H)-ylidene) (Hydroxy)methyl]butanal (**15b**).* Yellow solid; mp 101−104 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 3442, 1712, 1639, 1592, 1255, 1220; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.75 (d, J = 1.0 Hz, 1H), 7.90−7.86 (m, 2H), 7.80−7.74 (m, 2H), 4.58 (dd, J_1 = 8.2 Hz, J_2 = 5.8 Hz, 1H), 2.20−2.09 (m,1H), 2.07−1.97 (m, 1H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.8, 196.5, 180.4, 171.8, 140.8, 138.2, 135.5, 134.6, 122.2, 122.9, 110.3, 56.5, 20.3, 11.8; ESI negative 243 (M − H)$^+$; Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 68.68; H, 4.80.

*Reaction of Ylide **4** with (Cyclohex-1-en-1-yloxy)trimethylsilane (**30**). Method I.* A suspension of ylide **4** (376 mg, 1 mmol) in (cyclohex-1-en-1-yloxy)trimethylsilane (3 mL) was stirred under reflux for 75 min. The crystallization of any product by treatment with CH_2Cl_2/PE or Et_2O/PE was unsuccessful. The reaction mixture was concentrated in vacuum and separated by column chromatography to afford, in order of elution, compound **31** (83 mg, 33%) and the hydrate **32**·H_2O (75 mg, 26%).

Method II. A mixture of ylide **4** (376 mg 1 mmol) and (cyclohex-1-en-1-yloxy)trimethylsilane (2 mL) in CH_2Cl_2 (2 mL) was irradiated in the MW oven at 90 °C for 3 min. The mixture was treated with Et_2O/PE, and product **33** was precipitated and collected by filtration (83 mg, yield 28%). The filtrate was concentrated and subjected to column chromatography to afford the hydrate **32 · H_2O** in yield 39% (107 mg).

Protocol A: At 70 °C, a large part of the starting ylide **4b** (132 mg, 35%) remained unchanged and was separated from the reaction mixture by filtration. After concentration of the filtrate and treatment of the residue with CH_2Cl_2/PE, pure product **32** (74 mg, 28%) was crystallized and isolated by filtration.

Protocol B: At 100 °C, the products **32** and **33** were detected (^{1}H NMR) in the reaction mixture. Treatment of the concentrated reaction mixture with CH_2Cl_2/petroleum ether resulted in crystals of pure compound **32**, collected by filtration (isolated yield 30%, 40 mg). The isolation of compound **33** by crystallization was unsuccessful. The estimated yields for **32** and **33** are recorded in Table 1.

Protocol C: From the reaction conducted at 140 °C, a large part of compound **31** (49 mg, 39%) precipitated upon treatment of the concentrated reaction mixture with Et_2O/PE and collected by filtration.

*2-[Hydroxy(2-methoxy-3,4-dihydro-2H-pyran-5-yl)methylene]-1H-indene-1,3(2H)-dione (**31**).* Yellow solid, mp 210−214 °C (Et_2O/PE); IR (KBr) cm^{-1} 1717, 1649, 1102; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.69−7.63 (m, 1H), 7.57−7.45 (m, 3H), 2.73−2.65 (m, 2H), 2.58−2.44 (m, 2H), 1.95−1.82 (m, 2H), 1.77−1.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.0, 178.0, 173.0, 162.2, 135.0, 133.5, 133.0, 132.4, 126.9, 123.7, 120.5, 113.2, 27.4, 21.8, 21.2, 21.1; ESI positive 253 (M + H)$^+$, 275 (M + Na)$^+$; Anal. calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.30; H, 4.78.

*2-[(2-Oxocyclohexyl)carbonyl]-1H-indene-1,3(2H)-dione (**32**).* Yellow solid; mp 90−92 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 3431, 1719, 1621, 1588; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88−7.79 (m, 2H), 7.74−7.69 (m, 2H), 4.62 (dd, J_1 = 12.3 Hz, J_2 = 5.9 Hz,1H), 2.61−2.52 (m, 2H), 2.31−2.17 (m, 3H), 2.08−2.00 (m, 1H), 1.92−1.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.4, 196.8, 188.5, 182.4, 140.7, 138.3, 135.2, 134.3, 122.9, 122.7, 109.6, 54.0, 45.0, 29.1, 26.9, 24.1; ESI positive 271 (M + H)$^+$; Anal. calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.90; H, 5.12.

*2-[(2-Oxocyclohexyl)carbonyl]-1H-indene-1,3(2H)-dione hydrate (**32 · H_2O**),.* Yellow solid; mp >300 °C (lit.[10] mp >320 °C).

*5a-[(Trimethylsilyl)oxy]-5a,6,7,8,9,9a-hexahydroindeno[1,2-b]-chromene-10,11-dione (**33**).* Yellow solid; mp 117−120 °C (Et_2O/PE); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67−7.59 (m, 1H), 7.56−7.48 (m, 2H), 7.46−7.41 (m, 1H), 2.63−2.50 (m, 1H), 2.41−2.20 (m, 2H), 2.18−1.74 (m, 3H), 1.65−1.42 (m, 2H), 1.37−1.13 (m, 1H), 0.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = δ 187.8, 186.1, 183.5, 135.6, 133.7, 133.6, 133.0, 122.9, 120.9, 111.9, 107.8, 54.3, 37.5, 24.4, 22.9, 21.8, 1.3; ESI positive 275 [(M−Me_3SiOH) + Na]$^+$. Anal. calcd for $C_{19}H_{22}O_4Si$: C, 66.64; H, 6.48. Found: C, 66.83; H, 6.29.

*Reaction of Ylide **4** with 2-Methoxyprop-1-ene (**34**). Method I.* A mixture of ylide **4** (376 mg, 1 mmol) and 2-methoxyprop-1-ene (1 mL) in CH_2Cl_2 (3 mL) was stirred under reflux for 6 h. The unreacted ylide (300 mg, 80%) was removed from the reaction mixture by filtration, and the filtrate was concentrated. Treatment of the residue with CH_2Cl_2/PE resulted in crystallization of compound **35** (27 mg, 11%).

Method II. Protocol A: Treatment of the concentrated reaction mixture with CH_2Cl_2/PE resulted in crystallization of compound **35** (184 mg, 76%)

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

Protocol B: After work up, compound **35** (98 mg, 80%) was crystallized by treatment of the concentrated reaction mixture with CH_2Cl_2/PE and isolated by filtration.

*2-(1-Hydroxy-3-methoxybut-2-en-1-ylidene)-1H-indene-1,3(2H)-dione (**35**).* Yellow solid; mp 192−195 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 3438, 1693, 1634, 1606, 1263, 1103, 1053; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76−7.71 (m, 2H), 7.67−7.59 (m, 3H), 6.74 (s, 1H), 3.88 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 189.0, 177.6, 177.3, 140.4, 138.3, 134.1, 133.3, 122.0, 121.7, 105.3, 92.6, 56.7, 21.8; ESI positive 227 $(M + H)^+$, 249 $(M + Na)^+$; Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 69.01; H, 4.76.

*Reaction of Ylide **4** with 2-Methoxy-3,4-dihydro-2H-pyran (**36**). Method I.* A suspension of ylide **4** (376 mg, 1 mmol) in 2-methoxy-3,4-dihydro-2*H*-pyran (2 mL) was heated at 80 °C for 20 min. The excess of vinyl ether was removed by evaporation. Treatment of the residue with CH_2Cl_2/petroleum ether resulted in the precipitation of a mixture of products **37** and **38**. This mixture was subjected to column chromatography (silica gel, petroleum ether/ethyl acetate 3:1) to afford product **38** (97 mg, 34%), which was further crystallized by treatment with CH_2Cl_2/PE.

Method II. Protocol A: Treatment of the concentrated reaction mixture with CH_2Cl_2/PE resulted in the precipitation of an inseparable 1:2 mixture of products **37** and **38** (206 mg).

Protocol B: After the previously described work up, a mixture (1:6) of compounds **37** and **38** (100 mg) was precipitated.

Protocol C: Crystallization of the concentrated reaction mixture with CH_2Cl_2/PE afforded product **38** (90 mg, 63%).

(4aR,11aS*)-2-Methoxy-4,4a-dihydro-2H-indeno[1,2-b]pyrano-[3,2-e]pyran-5,6(3H,11aH)-dione (**37**).* ^1H and ^{13}C NMR spectra of **37**, as they result by subtraction of the corresponding peaks for compound **38** from the spectra of their mixture. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.66−7.61 (m, 1H), 7.59−7.55 (m, 3H), 6.18 (d, J = 3.3 Hz, 1H), 4.97 (dd, J_1 = 5.5 Hz, J_2 = 4.3 Hz, 1H), 3.58 (s, 3H), 2.82−2.78 (m, 1H), 2.20−2.12 (m, 1H), 2.10−2.00 (m, 1H), 1.95−1.86 (m, 1H), 1.69−1.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.4, 185.8, 185.3, 134.8, 134.3, 133.9, 133.2, 123.1, 121.7, 106.9, 102,4, 100.9, 56.3, 45.5, 27.3, 19.1.

*2-(Hydroxy(2-methoxy-3,4-dihydro-2H-pyran-5-yl)methylene)-1H-indene-1,3(2H)-dione (**38**).* Light-orange solid; mp 84−87 °C (CH_2Cl_2/PE); IR (KBr) cm^{-1} 3435, 1686, 1622, 1600, 1227, 1180; ^1H NMR (500 MHz, $CDCl_3$): δ = 15.70 (brs, 1H), 8.96 (s, 1H), 7.71−7.63 (m, 2H), 7.60−7.50 (m, 2H), 5.08 (dd appearing as t, J = 3.1 Hz, 1H), 3.48 (s, 3H), 2.51−2.38 (m, 2H), 2.04−1.94 (m, 1H), 1.90−1.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.8, 187.7, 181.6, 160.0, 139.4, 137.3, 134.4, 133.4, 122.3, 121.7, 110.3, 105.1, 99.8, 56.5, 25.6, 15.1; ESI negative 285 $(M - H)^+$; Anal. calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 66.88; H, 5.22.

*Acid-Catalyzed Transformation of 2-Isobutoxy-2,3-dihydroindeno[1,2-b]pyran-4,5-dione (**12a**) to (E)-2-(1,3-Dihydroxyallylidene)-1H-indene-1,3(2H)-dione (**15a**).* A catalytic amount of trifluoroacetic acid (TFA) was added to a solution of 2-isobutoxy-2,3-dihydroindeno[1,2-*b*]pyran-4,5-dione (**12a**) (0.04 g, 0.15 mmol) in CH_2Cl_2 (2 mL), and the mixture remained at rt for 2 days. Compound **15a** was precipitated upon treatment of the concentrated reaction mixture with CH_2Cl_2/PE and collected by filtration (15 mg, 44% yield).

*(E)-2-(1,3-Dihydroxyallylidene)-1H-indene-1,3(2H)-dione (**15a**).* Yellow solid; mp >300 °C (dec); IR (KBr) cm^{-1} 3446, 1679, 1641, 1285, 1095; ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) δ = 8.06 (d, J = 12.1 Hz, 1H), 7.75−7.72 (m, 2H), 7.69−7.61 (m, 2H), 6.78 (d, J = 12.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ = 196.7, 188.5, 176.7, 164.5, 140.0, 138.0, 133.7, 132.9, 121.5, 121.2, 103.9, 98.1; ESI positive 239 $(M + Na)^+$; Anal. calcd for $C_{12}H_8O_4$: C, 66.67; H, 3.73. Found: C, 66.83; H, 4.00.

*Thermal Isomerization of 2-Isobutoxy-2,3-dihydroindeno[1,2-b]pyran-4,5-dione (**12a**) to 2-(1-Hydroxy-3-isobutoxyallylidene)-1H-indene-1,3(2H)-dione (**13a**).* 2-Isobutoxy-2,3-dihydroindeno[1,2-*b*]pyran-4,5-dione (**12a**) (41 mg, 0.15 mmol) was heated under reflux in dimethoxyethane (DME, 2 mL) for 4.5 h. DME was evaporated, and the residue was subjected to column chromatography to afford compound **13a** (38 mg, 93%).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02872.

^1H and ^{13}C NMR spectra for all new compounds and complete ref 29. Results from the computational study: Cartesian coordinates, structures and energies for all stationary point geometries found in the PESs of **5** with the electron-rich dienophiles, as well as those of all reagents for both methods used, are compiled in Tables S1−S9 and Figure S2 (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: malamido@chem.auth.gr Phone: (+30)2310 997874. Fax: (+30) 2310 997679.

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Tidwell, T. T. *Ketenes*; John Wiley & Sons: Hoboken, NJ, 2006.
(2) Wentrup, C.; Heilmayer, W.; Kollenz, G. *Synthesis* **1994**, *1994*, 1219−1248.
(3) Kollenz, G.; Heilmayer, W.; Kappe, C. O.; Wallfish, B.; Wentrup, C. *Croat. Chem. Acta* **2001**, *74*, 815−823.
(4) Kappe, C. O.; Evans, R. A.; Kennard, C. H. L.; Wentrup, C. *J. Am. Chem. Soc.* **1991**, *113*, 4234−4237.
(5) Kappe, C. O.; Färber, G.; Wentrup, C.; Kollenz, G. *J. Org. Chem.* **1992**, *57*, 7078−7083.
(6) Kappe, C. O.; Kollenz, G.; Fabian, W. M. F.; Wentrup, C.; Färber, G. *J. Org. Chem.* **1993**, *58*, 3361−3367.
(7) Stadler, A.; Zangger, K.; Belaj, F.; Kollenz, G. *Tetrahedron* **2001**, *57*, 6757−6763.
(8) Wallfisch, B. C.; Belaj, F.; Wentrup, C.; Kappe, C. O. *J. Chem. Soc., Perkin Trans. I* **2002**, 599−605.
(9) Malamidou-Xenikaki, E.; Spyroudis, S. *Synlett* **2008**, *2008*, 2725−2740.
(10) Koulouri, S.; Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M. *J. Org. Chem.* **2005**, *70*, 8780−8784.
(11) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Krautscheid, H. *J. Org. Chem.* **2007**, *72*, 502−508.
(12) Bakalbassis, E. G.; Spyroudis, S.; Tsipis, C. A. *Eur. J. Org. Chem.* **2008**, *2008*, 1783−1788.
(13) Bakalbassis, E. G.; Malamidou-Xenikaki, E.; Spyroudis, S.; Xantheas, S. *J. Org. Chem.* **2010**, *75*, 5499−5504.
(14) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Krautscheid, H. *J. Org. Chem.* **2008**, *73*, 8392−8397.
(15) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M.; Hatdjipavlou-Litina, D. *J. Org. Chem.* **2009**, *74*, 7315−7321.
(16) Tsanakopoulou, M.; Cottin, T.; Büttner, A.; Sarli, V.; Malamidou-Xenikaki, E.; Spyroudis, S.; Giannis, A. *ChemMedChem* **2008**, *3*, 429−433.
(17) Malamidou-Xenikaki, E.; Spyroudis, S.; Tsanakopoulou, M. *J. Org. Chem.* **2003**, *68*, 5627−5631.
(18) Spagou, K.; Malamidou-Xenikaki, E.; Spyroudis, S. *Molecules* **2005**, *10*, 226−237.
(19) Wenkert, C.; Ananthanarayan, T. P.; Ferreira, V. F.; Hoffmann, M. G.; Kim, H. *J. Org. Chem.* **1990**, *55*, 4975−4976.
(20) Zawacki, F. J.; Crimmins, M. T. *Tetrahedron Lett.* **1996**, *37*, 6499−6502.
(21) Sato, M.; Ban, H.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 6689−6690.
(22) Crimmins, M. T.; Washburn, D. G.; Zawacki, F. J. *Org. Synth.* **1999**, *77*, 114−120.
(23) Toda, J.; Saitoh, T.; Oyama, T.; Horiguchi, Y.; Sano, T. *Heterocycles* **1996**, *43*, 2457−2464.

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398

(24) Saripinar, E.; Guzel, Y.; Onal, Z.; Ilhan, I. O.; Akcamur, Y. *J. Chem. Soc. Pakistan* **2000**, *22*, 308−317.
(25) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785.
(26) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.
(27) (a) Ess, D. H.; Jones, G. O.; Houk, K. N. *Adv. Synth. Catal.* **2006**, *348*, 2337. (b) Domingo, L. R. *RSC Adv.* **2014**, *4*, 32415.
(28) (a) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214. (b) Schlegel, H. B. Geometry Optimization on Potential Energy Surface. In *Modern Electronic Structure Theory*, Yarkony, D. R., Ed.; World Scientific Publishing: Singapore, 1994.
(29) Frisch, M. J.; et al. *Gaussian 09*, Revision B.01; Gaussian, Inc.: Wallingford, CT, 2010.
(30) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161.
(31) (a) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154. (b) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523.
(32) (a) Becke, A. D. *Phys. Rev. A: At., Mol., Opt. Phys.* **1988**, *38*, 3098. (b) Perdew, J. P. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1986**, *33*, 8822.
(33) (a) Parr, R. G.; von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922. (b) Pérez, P.; Domingo, L. R.; Aizman, A.; Contreras, R. In *Theoretical Aspects of Chemical Reactivity*; Toro-Labbé, T., Ed.; Elsevier Science: New York, 2006, Vol. *19*, pp 167−238. (c) Domingo, L. R.; Chamorro, E.; Pérez, P. *J. Org. Chem.* **2008**, *73*, 4615. (d) Domingo, L. R.; Sáez, J. A. *Org. Biomol. Chem.* **2009**, *7*, 3576.
(34) (a) Goldstein, M. J., Jr.; Thayer, G. L. *J. Am. Chem. Soc.* **1965**, *87*, 1933. (b) Domingo, L. R.; Saéz, J. A.; Zaragozá, R. J.; Arnó, M. *J. Org. Chem.* **2008**, *73*, 8791.
(35) Domingo, L. R.; Arnó, M.; Andres, J. *J. Org. Chem.* **1999**, *64*, 5867.
(36) Thasana, N.; Ruchirawat, S. *Tetrahedron Lett.* **2002**, *43*, 4515−4517.
(37) Mokesch, S.; Novak, M. S.; Roller, A.; Jakupec, M. A.; Kandioller, W.; Keppler, B. K. *Organometallics* **2015**, *34*, 848−857.
(38) Hatzigrigoriou, H.; Spyroudis, S.; Varvoglis, A. *Liebigs Ann. Chem.* **1989**, *1989*, 167.

DOI: 10.1021/acs.joc.5b02872
J. Org. Chem. 2016, 81, 2383−2398