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Synthetic Methods

Reactivity of *N*-Substituted *Exo*-oxazolidin-2-one Dienes with Naphthalene Chalcones and Cyclic 1,3-Dicarbonyl Compounds

Salvador Mastachi-Loza,[a] Tania I. Ramírez-Candelero,[a] Carlos González-Romero,[a] Eduardo Díaz-Torres,[a] Aydeé Fuentes-Benítes,*[a] and Joaquín Tamariz[b]

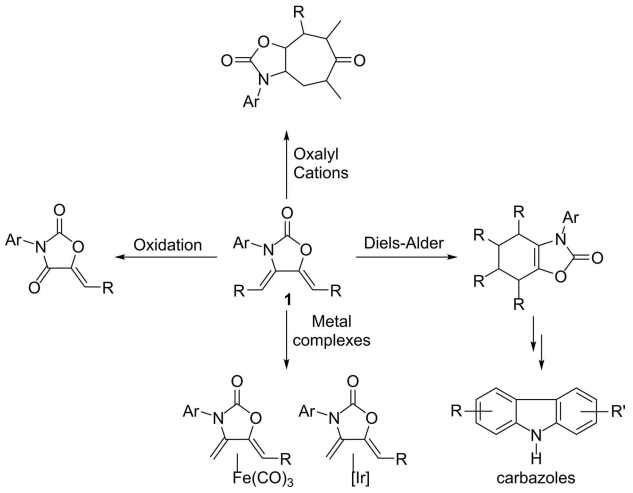
Abstract: The *N*-substituted *exo*-2-oxazolidinone dienes are versatile molecules that undergo a variety of reactions. To further explore this versatility, Diels-Alder reactions were carried out with novel naphthalene chalcones. Upon attempting the Diels-Alder reaction with 2-hydroxy-1,4-naphthoquinone, the formation of chromene unexpectedly took place via a formal [3+3] cycloaddition reaction. The observed reaction was then achieved with other 1,3-dicarbonyl compounds.

Introduction

The *N*-substituted *exo*-2-oxazolidinone dienes **1** are useful and versatile molecules that undergo a variety of reactions, including Diels-Alder cycloadditions,[1–4] [4+3] cycloadditions with oxalyl cations,[5] the formation of metal complexes[6–8] and oxidation to oxazolidine-2,4-diones.[9] These dienes have also been involved in the successful synthesis of natural carbazoles (Scheme 1).[10–13]

Dienes **1** are known to react with different dienophiles, particularly those substituted with electron withdrawing groups. Among the possible dienophiles are chalcones, molecules containing a *trans*-1,3-diaryl-2-propen-1-one as the chemical scaffold.[14,15] This framework is widespread in nature, being found in compounds within vegetables, fruits and other plants.[15–18] Owing to their electron deficient double bond, chalcones are excellent dienophiles, readily reacting with diverse dienes.[19–23]

On the other hand, 1,2- and 1,4-naphthoquinones are a group of compounds derived from naphthalene, with the structure of fully conjugated diones.[24] These naturally-occurring compounds[25,26] serve as natural oxidation-reduction reagents. One example is vitamin K, comprised of a naphthoquinone skeleton that plays a vital role in several biological processes.[27] Moreover, naphthoquinones have been used as dienophiles in Diels-Alder cycloadditions for the construction of important molecules.[28–30]



Scheme 1. Previously reported reactions of *N*-substituted *exo*-2-oxazolidinone dienes **1**.

To improve the synthetic scope for dienes **1**, we herein describe Diels-Alder reactions with novel 1,4-dimethoxynaphthalene chalcones. Moreover, we present the case of an attempted Diels-Alder reaction with 2-hydroxy-1,4-naphthoquinone that led to a chromene compound by a formal [3+3] cycloaddition. This reaction was further explored with other 1,3-dicarbonyl compounds.

Results and Discussion

The first objective was to prepare new benzoxazole-2-ones **2** with a naphthoquinone moiety. The synthetic approach was the oxidation of compound **3** which had been generated by a Diels-Alder reaction between diene **1a** and chalcones **4** (Scheme 2).

The *N*-substituted *exo*-2-oxazolidinone diene **1a** was prepared by condensation of 2,3-pentanedione with the corre-

[a] *S. Mastachi-Loza, T. I. Ramírez-Candelero, C. González-Romero, E. Díaz-Torres, A. Fuentes-Benítes*
Departamento de Química Orgánica
Facultad de Química, Universidad Autónoma del Estado de México
Paseo Tollocan y ColónS/N, 50000, Toluca, Estado de México, México
E-mail: mpagfuentesb@uaemex.mx

[b] *J. Tamariz*
Escuela Nacional de Ciencias Biológicas
Instituto Politécnico Nacional
Prol. Carpio y Plan de AyalaS/N, 11340, CDMX, México

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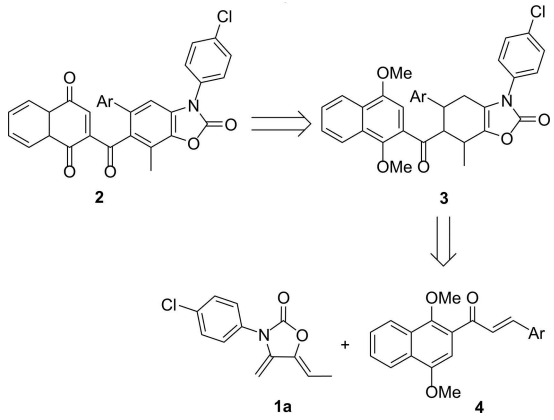
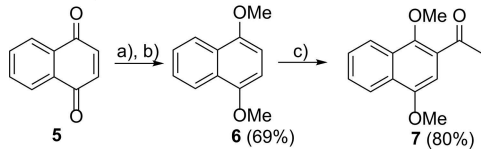


Scheme 2. Retrosynthesis for target compounds **2**.

sponding aryl isocyanate in the presence of triethylamine as the base, employing a well-known method.[1] The synthesis of chalcones **4**, to our knowledge being reported for the first time, began with the reduction of naphthoquinone (**5**) by using $SnCl_2 \cdot 2H_2O$ in concentrated HCl. Subsequently, the resulting 1,4-naphthohydroquinone was methylated with MeI and K_2CO_3, furnishing **6** in good yield. Diverse techniques were assayed for the acetylation of compound **6**, but common methods, such as acetyl chloride in the presence of $AlCl_3$, gave multiple acylation products. However, by using a mixture of trifluoroacetic anhydride and acetic acid,[31] 2-acetyl-1,4-dimethoxy naphthalene (**7**) was provided in good yield (Scheme 3).

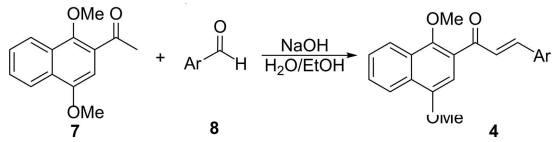


Scheme 3. Reaction conditions: a) $SnCl_2 \cdot 2H_2O$, HCl, MeOH, reflux, 3 h. b) MeI, K_2CO_3, DMF, 50 °C, overnight. c) TFAA, AcOH, 60 °C, 3 h.

The desired key naphthoquinone 7 underwent aldol condensation with aromatic aldehydes in the presence of NaOH as the base, affording the series of novel naphthalene chalcones **4a–e** in good to moderate yields (Table 1).

Subsequently, with toluene as solvent, the Diels-Alder cycloaddition between **1a** (1 mmol) and chalcones **4a–e** (1 mmol) was carried out in an Ace-glass pressure tube by heating at 180 °C for 24 h. This method furnished tetrahydrobenzoxazol-2-ones **3** in good yields. This reaction was regioselective, as only the *ortho* isomers (relative to the methyl and carbonyl functional groups) were produced. A detailed NMR analysis of the sole purified fraction of adducts **3** revealed a mixture of the two diastereoisomers **9** and **10** (Table 2). In all the reactions, the major diastereoisomers were the *endo* adducts **10a–e**. The relative configuration for both isomers was assigned in accordance with previous studies that examined oxazolidin-2-one dienes 1 in Diels-Alder reactions.[1]

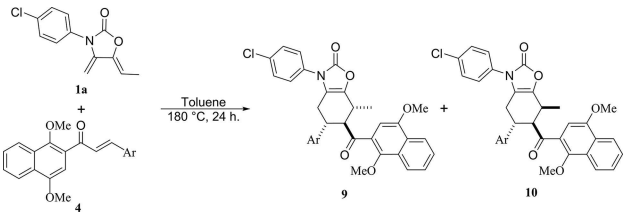
Table 1. Synthesis of novel chalcones **4**.[a]



Compound	Ar	Yield (%)[b]	m.p. (°C)
4a	4-methoxyphenyl	91	99–100
4b	4-methylthiophenyl	76	85–86
4c	2-thienyl	79	139–140
4d	2,4-dichlorophenyl	77	108–109
4e	phenyl	66	oil

[a] **7** (5 mmol), **8** (5 mmol), EtOH (20 mL), NaOH (25 mL, 10% aq.) reacted for 0.5–1 h at r.t. [b] After crystallization from hot EtOH.

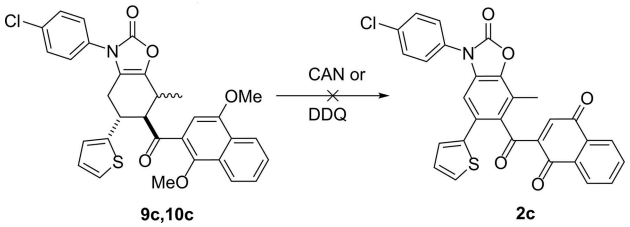
Table 2. Preparation of diastereoisomeric Diels-Alder adducts 4,5,6,7-tetrahydrobenzoxazol-2-ones **9**/**10**.



Adducts	Ar	Yield (%)[a]	Ratio[b] 9/10
9a, **10a**	4-methoxyphenyl	72	40:60
9b, **10b**	4-methylthiophenyl	78	39:61
9c, **10c**	2-thienyl	72	16:84
9d, **10d**	2,4-dichlorophenyl	64	2:98
9e, **10e**	phenyl	74	20:80

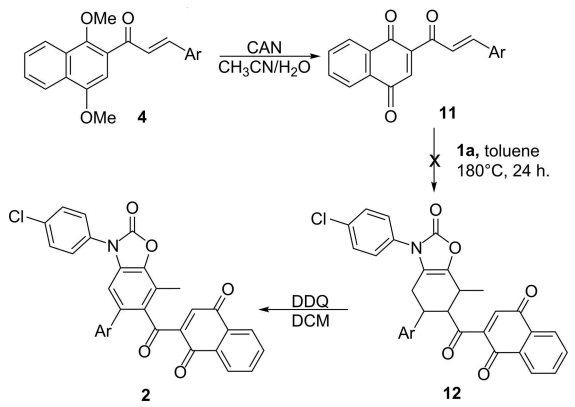
[a] For diastereoisomer mixture. [b] Determined by ^{1}H NMR.

Attempts to aromatize the cyclohexyl moiety of the mixture of adducts **9c**/**10c**, as well as to oxidize the 1,4-dimethoxynaphthalene moiety to 1,4-naphthoquinone **2c** by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or ceric ammonium nitrate (CAN) were unsuccessful, and a complex mixture of products was observed (Scheme 4).



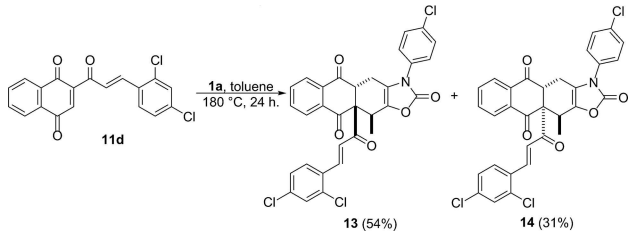
Scheme 4. Attempts to aromatize **9c**/**10c**.

After reviewing the proposed pathway, we decided to oxidize chalcones **4a–e** before carrying out the Diels-Alder cycloaddition, which was followed by the oxidative aromatization with DDQ to provide the desired product **2** (Scheme 5).



Scheme 5. Alternative pathway to synthesize **2**.

Oxidation of chalcone **4d** (1 mmol) using CAN (3 mmol) in CH_3CN/H_2O and stirring at room temperature for 30 min. gave the corresponding 1,4-naphthoquinone **11d** in high yield (96%). Rather than providing the desired product **12**, however, the Diels-Alder cycloaddition between **11d** and **1a** afforded a pair of diastereoisomers, **13**/**14** (64:36), in 85% overall yield. They were separated by purification with column chromatography (Scheme 6).



Scheme 6. Diels-Alder cycloaddition between **1a** and **11d**.

Notably, only the *ortho* regioisomer (relative to the *gem* disubstituted carbon of dienophile **11d** and the methyl substituted terminal carbon atom of diene **1a**) was furnished, and the *exo* isomer (considering the quinone moiety of the dienophile **11d**) was the major diastereoisomer. Moreover, this cycloaddition proceeded with high chemoselectivity since the reaction occurred at the naphthoquinone moiety as the dienophile rather than propen-1-one as the dienophile. The higher reactivity of the quinone moiety as the dienophile is probably due to the presence of three electron-withdrawing groups (two carbonyl groups of the quinone functional group and the third of the chalcone component) that strongly activate the double bond.[32]

Characterization for compounds **13** and **14** was achieved by ^{1}H NMR, ^{13}C NMR and 2D NMR experiments (COSY, NOESY, HSQC and HMBC). In the ^{1}H NMR spectra, both products showed two doublet signals ($J \approx 15$ Hz) at the range of 6.7–8.0 ppm. These were attributed to the vinyl protons of the propen-1-one moiety, indicating their (*E*) configuration and supporting the overall chemoselectivity. Meanwhile, ^{13}C NMR exhibited the presence of three carbonyl groups (190–195 ppm C_5, C_{10}, C_{13}) and the carbamate carbonyl group in 153–154 ppm (C_2) (Figure 1a). The assignment of the signals for protons H_4,

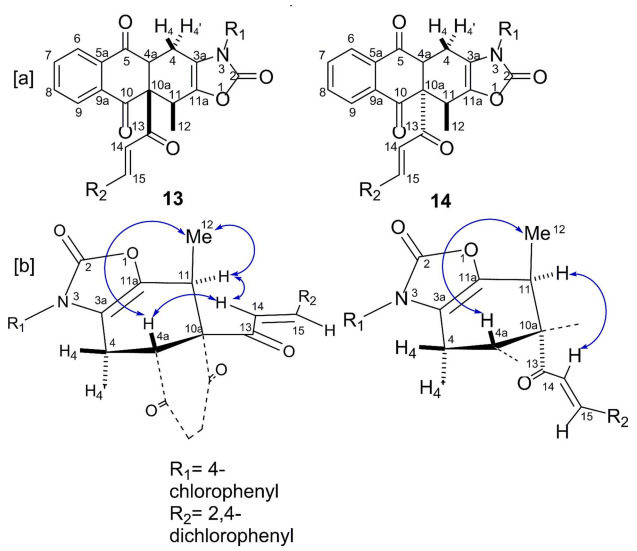
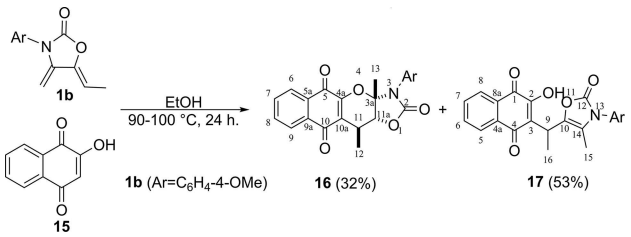


Figure 1. [a] Structure of **13** and **14**. [b] NOESY correlations in **13** and **14**.

H_{4a}, H_{11} and H_{12} and their correlation within the cyclohexene moiety provided the key evidence that allowed the relative configuration of both products to be established. For instance, the relative configuration for H_{4a} in **13** was identified by determining the coupling constants of H_4 and $H_{4'}$ with H_{4a}. This signal is displayed as a doublet of doublet (dd, $J = 11.3$, 5.6 Hz). The large coupling constant corresponds to the $H_{4a}ax$-$H_{4'}ax$ coupling, and the small one to the $H_{4a}ax$-H_4eq coupling (Figure 1b). The C_{12} methyl group configuration was revealed by a NOESY experiment. Thus, proton H_{4a} exhibits cross peak/diagonal peak signals with proton H_{12}, meaning that the methyl group is also *axial*. Although this correlation is illustrated in **14** as well, the difference between the two isomers was established based on the correlations between the vinyl proton H_{14} and the cyclohexenyl protons. In the NOESY experiment for isomer **13**, cross peak/diagonal peak signals were displayed with protons H_{4a} (weak), H_{11} (strong) and H_{12} (strong), indicating that the prop-3-en-1-one group has a relative *cis* configuration regarding those protons. On the contrary, proton H_{14} for isomer **14** only displays cross peak/diagonal peak signals with proton H_{11}, suggesting a relative *trans* configuration with regarding proton H_{4a} and methyl group H_{12} (Figure 1b).

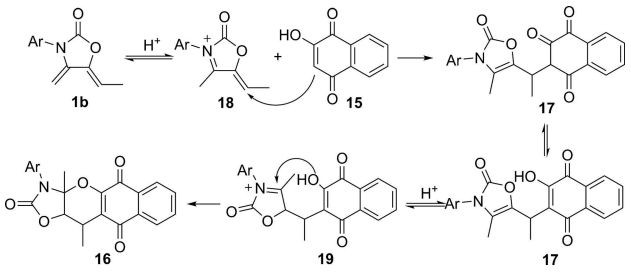
Due to the abovementioned results, other cycloadditions were tested between dienes **1** and naphthoquinone derivatives in an attempt to obtain a series of anthraquinones. Accordingly, **1b** was reacted with 2-hydroxy-1,4-naphthalene (**15**) in EtOH and heated at 90–100 °C for 24 h. Instead of the expected Diels-Alder adducts, new compounds were isolated and characterized, being chromene **16** and naphthoquinone **17** (Scheme 7).

Apparently, chromene **16** was formed through a formal [3+3] cycloaddition reaction. This type of annulation has been



Scheme 7. Unexpected cycloaddition between **1a** and **15**.

employed for the construction of a variety of complex heterocycles,[33] and usually involves a condensation between α,β-unsaturated carbonyl compounds or α,β-unsaturated iminium salts (*in situ* generated) with 1,3-dicarbonyl compounds or β-enaminones.[34–37] Mechanistically, the process depends on the type of substrate used. It is a two-step reaction, in which two pathways are competing with each other: (a) a 1,2-addition vs. 1,4-addition, and (b) a *C*-addition vs. the *O*-addition.[38] Considering the presence of compound **17**, a plausible mechanism for the formation of **16** can be proposed. Dienes **1a** or **1b** undergo isomerization under the mild acidic conditions, as described in previous studies,[39,40] inducing the formation of iminium salt **18**. The latter suffers a *C*-1,4-addition by the *enol* moiety of **15** to form intermediate **17**. After formation of iminium salt **19**, the ring closure takes place by an *O*-1,2-addition, promoting the formation of chromene **16** (Scheme 8).

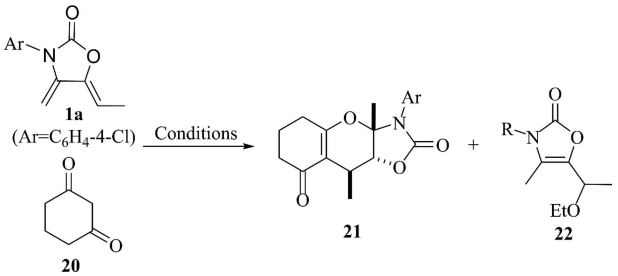


Scheme 8. Proposed mechanism for the synthesis of **16**.

The characterization of compounds **16** and **17** was achieved by ^{1}H NMR, ^{13}C NMR and 2D NMR experiments (NOESY, COSY, HSQC and HMBC). In the ^{1}H NMR spectrum of **17**, proton H_9 appears at 4.59 ppm as a quartet (J = 7.2 Hz), which is consistent with the absence of a vinylic proton in C_3 and the formation of the *enol* tautomer. Furthermore, the ^{13}C NMR spectrum displays a signal at 26.28 ppm attributed to C_9. This chemical shift would be expected for allylic carbons. In the case of the ^{13}C NMR spectrum of **16**, the signal of carbon C_{3a} is found at 93.61 ppm, which is consistent with a deshielding effect generated by adjacent O and N atoms. Likewise, proton H_{11} displays a crosspeak correlation with carbon C_{10} in the HMBC experiment. Interestingly, the ring closure of **16** was stereoselective, evidenced by the fact that only one diastereomer was observed. The relative configuration was established by a NOESY experiment, where H_{13} displays cross peak/diagonal peak signals with H_{12} and H_{11a}, meaning that methyl and methine protons are *cis* relative to each other. The *syn* relative configuration of the angular methyl group (C_{13}) and the secondary methyl group (C_{12}) is probably due to the steric repulsion and ring strain during the dihydropyran ring formation (from 19 to 16). This cyclization step leads to the formation of a heterocyclic hydrindane system (oxazolidin-2-one and dihydropyran rings), in which the *cis* bicyclic fusion is more stable than the *trans* one. This configuration induces the C_{12} methyl group to adopt a relative configuration that is *anti* with respect to the oxazolidin-2-one ring, and consequently *syn* with respect to the C_{13} methyl group.

Regarding the scope of the reaction, previous reports suggest that the formal [3+3] cycloaddition occurs with a variety of 1,3-dicarbonyl compounds.[33] To explore this idea, the annulation reaction between 1,3-cyclohexanedione (**20**) and diene **1a** was carried out, affording the expected product **21** and the new by-product **22**, the latter formed in a higher ratio. The use of AcOEt as solvent led to an increased yield of the desire chromene **21**, although the reaction was incomplete even after 48 h. Considering the proposed mechanism, acidic catalyst was employed (conc. HCl) in the presence of a proper solvent (THF), providing the desired chromene **21** in better yield without any side products (Table 3, entry 3). Moreover, no

Table 3. Reaction conditions[a] for synthesis of chromene **21**.



Entry	Solvent	Temp. (°C)	Time	Cat.	21 (%)	22 (%)
1	EtOH	90–100	24 h	–	12	65
2	AcOEt	90–100	48 h[b]	–	34	–
3	THF	90–100	24 h	HCl[c]	59	–

[a] **1a** (1 mmol), **20** (1 mmol) and 4 mL of solvent for 24 h. [b] No reaction completion ocurred. [c] 0.1 mL of concentrated solution.

reaction intermediaries were detected, which would appear to indicate a complete cyclization to give **21** as a single regio- and diastereoisomer (with a *cis* relative configuration, as formerly described for the pyran ring of **16**).

Having found the improved reaction conditions, other 1,3-dicarbonyl compounds were evaluated. As shown in Table 4, different chromenes were obtained by formal [3+3] cycloaddition with dienes **1a** and **1b**.

It is notable that for almost all the compounds, including **15**, no open intermediate was isolated (except for compound **33**), and the relative configuration for the fused-pyran ring was always the same.

Table 4. Synthesized chromenes by formal [3 + 3] cycloaddition.[a]

1a, Ar= 4-chlorophenyl
1b, Ar= 4-methoxyphenyl

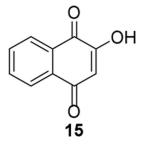
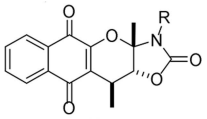
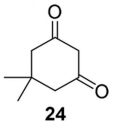
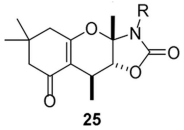
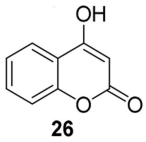
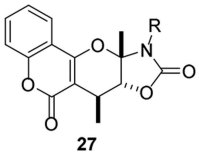
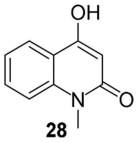
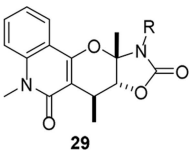
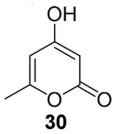
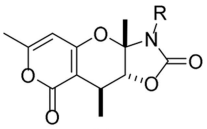
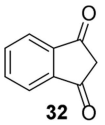
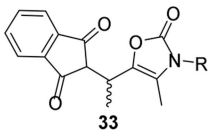
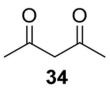
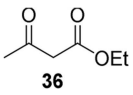
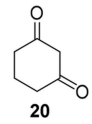
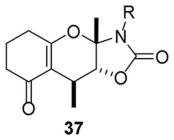
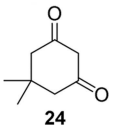
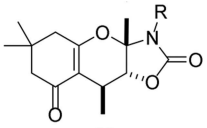
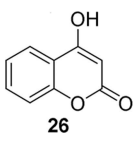
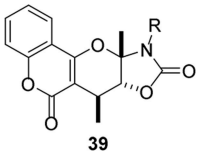
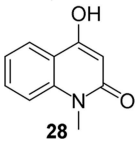
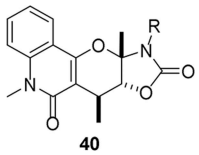
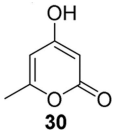
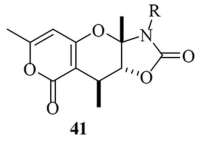
Diene	1,3-Dicarbonyl Compound	Product	Yield (%)[b]
1 a	 15	 23	54
1 a	 24	 25	55
1 a	 26	 27	48
1 a	 28	 29	71
1 a	 30	 31	47
1 a	 32	 33	43
1 a	 34	ND[c]	–
1 a	 36	ND[c]	–
1 b	 20	 37	88
1 b	 24	 38	64
1 b	 26	 39	80

Table 4. continued

1a, Ar= 4-chlorophenyl
1b, Ar= 4-methoxyphenyl

Diene	1,3-Dicarbonyl Compound	Product	Yield (%)[b]
1 b	 28	 40	58
1 b	 30	 41	56

[a] Reaction conditions: diene (1 mmol), 1,3-dicarbonyl compound (1mmol) and 0.1 mL conc. HCl at 90–100 °C for 24 h. [b] After purification. [c] Not detected, the structure for isomer 35 can be found in supporting information.

Regarding the use of acyclic β-*oxo* nucleophiles **34** and **36**, the isomeric diene **35** was identified as the main product, but without a [3 + 3] annulation. It is well known that dienes **1** tend to isomerize by a sigmatropic rearrangement upon heating and/or treatment under acidic conditions, forming the more stable isomer **35**.[3,39] Hence, the present results suggest that cyclic enols are needed to carry out the annulation process. Krasnaya[41] and Moorhoff[42] reported that with acyclic compounds, an equilibrated mixture of 1-oxatrienes and the desired pyranes is usually generated. This equilibrium is substrate dependent. In the few cases in which complete cyclization was achieved, the resulting yields were very low.[33] A similar behavior seems to be seen with the five-membered β-dicarbonylic substrate **32**, having only furnished the *C*-addition product **33** and isomer **35** (32%).

Conclusions

The preparation of novel chalcone derivatives **4** is herein described, as well as their use in the synthesis of 4,5,6,7-tetrahydrobenzoxazol-2-ones **9**/**10** and tetrahydroanthra[2,3-*d*]oxazole-2,5,10(3*H*)triones **13**/**14** by a highly regioselective Diels-Alder cycloaddition. An unexpected synthesis of chromeno[2,3-*d*]oxazol-2-ones via a formal [3 + 3] cycloaddition with 1,3-dicarbonyl compounds was found. This reaction proceeded with high regio- and stereoselectivity, although substrate limitations existed. Thus, the current results illustrate the versatility of *N*-substituted *exo*-2-oxazolidinone dienes **1** for the construction of diverse scaffolds with synthetic interest. Synthetic applications of these novel compounds are currently in process, and the results will be reported in due course.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Quinone · Diels-Alder · Benzoxazolone · Formal [3 + 3] cycloaddition · Chromene · Pyrane

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