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Diels−Alder Reactions of 3-Substituted Coumarins in Water and under High-Pressure Condition. An Uncatalyzed Route to Tetrahydro-6*H*-benzo[*c*]chromen-6-ones

Rugiada Girotti,† Assunta Marrocchi, Lucio Minuti,* Oriana Piermatti,†
Ferdinando Pizzo,*,† and Luigi Vaccaro†

*CEMIN “Centro di Eccellenza Materiali Innovativi Nanostrutturati”, and Dipartimento di Chimica,
Università degli Studi di Perugia, via Elce di Sotto 8, 06123 Perugia, Italy*

pizzo@unipg.it

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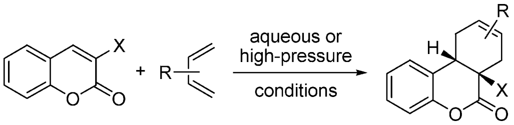
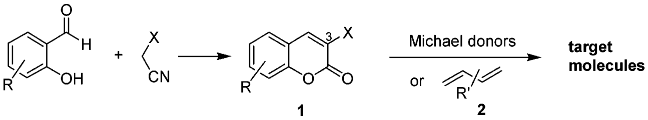


Diels−Alder reactions of 3-substituted coumarins **1a**−**g** with methyl-1,3-butadienes **2a**−**c** carried out in water alone and in CH_2Cl_2 under 9 kbar pressure are reported. In aqueous medium satisfactory results were obtained by operating at 150 °C, whereas under high pressure the cycloadditions were complete at 60−70 °C with excellent yields (85−95%). The reactions with isoprene (**2b**) always resulted in the exclusive formation of *para* cycloadducts, whereas with (*E*)-piperylene (**2c**) only *ortho* products were detected. The cycloaddition of 3-phenylsulfonylcoumarin (**1a**) with (*E*)-piperylene (**2c**) allowed the *endo* adduct to be obtained exclusively, whereas 3-carboxycoumarin (**1b**) reacted with **2c** to give a mixture of the corresponding *endo*/*exo* adducts in a 58:42 ratio in water and in a 45:55 ratio under high-pressure condition.

Introduction

In recent years we have been developing an efficient green organic chemistry by studying new environmentally friendly chemical processes. In our previous works we investigated the nucleophilic ring opening of 1,2-epoxide[1] and the [4 + 2] cycloadditions reactions of (*E*)-2-aryl-1-cyano-1-nitroethenes and 3-nitrocoumarins[2] by using water as reaction medium or under solvent-free condition (SFC). Currently, our interest is mainly focused on the development of innovative one-pot synthetic routes to target molecules incorporating the chromane subunit. Our approach to these heterocycles is based on the Knoevenagel condensation of salicylic aldehydes with substituted acetonitriles followed by a Michael addition or a [4 + 2] cycloaddition of the resulting 3-substituted coumarins **1** (Scheme 1).

SCHEME 1



Although we have already investigated the feasibility of Knoevenagel[3] and Michael steps[2a,b,d] within this synthetic strategy, the Diels−Alder cycloadditions of coumarins **1** are still largely unexplored, owing to low reactivity of the coumarin double bond. Diels−Alder reactions of 3-substituted coumarins with 1,3-dienes **2** are rare,[4] although this process permits the

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† CEMIN “Centro di Eccellenza Materiali Innovativi Nanostrutturati”.

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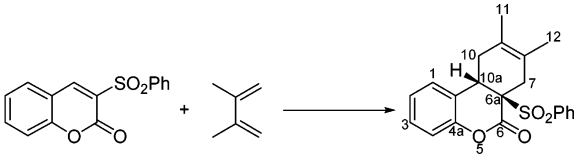
TABLE 1. Diels−Alder Reaction of 3-Phenylsulfonylcoumarin (1a) with 2,3-Dimethyl-1,3-butadiene (2a) under Various Reaction Conditions



1a **2a** **3a**

entry	medium	**2a** (equiv)	catalyst (mol %)	*P* (kbar)	*T* (°C)	*t* (h)	yield (%)[a]
1	CH_2Cl_2	4		9	60	15	90[b]
2	THF	4		9	60	15	50
3	THF/H_2O[c]	4		9	60	15	35
4	CH_2Cl_2	4			60	15	
5	CH_2Cl_2	4	$TiCl_4$·2THF (50%)		60	15	
6	CH_2Cl_2	4			150	15	60
7	SFC	4			60	15	
8	SFC	4	$TiCl_4$·2THF (50%)		60	15	
9	SFC	4	$AlCl_3$ (50%)		60	15	
10	SFC	4			150	15	80
11	H_2O	3			60	15	
12	H_2O	3	SDS (30%)		60	15	
13	H_2O	3	$AlCl_3$ (10%), SDS (30%)		60	15	
14	H_2O	3			150	6	70

[a] Yield of isolated **3a**. [b] Operating with 2 mol/equiv of diene **2a** or at 5 kbar pressure, the yields after 15 h were 60% and 26%, respectively. [c] THF/H_2O = 9:1.

preparation of tetrahydro-6*H*-benzo[*c*]chromen-6-ones as precursors of important molecules, such as functionalized biphenyls and cannabinoid derivatives. Since the presence of a substituent at C-3 position such as CN and CO_2R does not sufficiently activate the dienophilic system, these coumarins react with 1,3-dienes only at high temperature in a long reaction time, and the relative cycloadducts are often isolated in low yields. Sufficient activation has only been achieved in the case of 3-alkoxycarbonylcoumarins by using an excess of $ZnCl_2$ (1.2 equiv) and a large amount (44 equiv) of 1,3-dienes.[4a] In a recent paper from this laboratory, we have described the cycloadditions of 3-nitrocoumarins (**1**, X = NO_2) with various 1,3-butadienes **2** and the transformation of the obtained cycloadducts to the corresponding dihydrodibenzo[*b*,*d*]furans.[2c] Despite the activation by the strong electron-withdrawing nitro group, the hydroxy-substituted 3-nitrocoumarins in water or under SFC behave as poor dienophiles in [4 + 2] cycloadditions, reacting only at 150 °C with moderate yields. To our knowledge, alternative procedures for preparing tetrahydro-6*H*-benzo[*c*]chromen-6-ones are not available, but we believe that a more efficient approach to these aromatic heterocycles is necessary.

The activation by a Lewis acid catalyst could, in principle, allow the reactions of 3-substituted coumarins **1a**−**g** with 1,3-dienes **2a**−**c** to be realized, but quoting the literature[4a] an overstoichiometric amount of metal catalyst and/or a large excess of 1,3-diene **2a**−**c** are probably required to obtain satisfactory results. These conditions would make the procedure environmentally unsustainable due to the difficult and/or expensive recovery and disposal of the metal catalyst used.

It is known that high pressure strongly accelerates the Diels−Alder cycloadditions, allowing heat- and acid-sensitive and/or low reactive dienophiles or 1,3-dienes to be used.[5] High-pressure technique would allow these reactions to be performed under mild conditions with no need for any catalytic species, making the process chemically efficient and environmentally safe. Similarly, the high internal pressure of water is thought to be responsible for facilitating the Diels−Alder reaction, allowing faster and more stereoselective cycloadditions.[6]

With the intention to develop a new procedure to benzo[*c*]chromen-6-ones derivatives in this paper, we report the Diels−Alder cycloadditions of low reactive 3-substituted coumarins **1a**−**g** with methyl 1,3-butadienes **2a**−**c**, using water as reaction medium or operating under 9 kbar pressure.

Results and Discussion

The Diels−Alder reaction of 3-phenylsulfonylcoumarin (**1a**) with 2,3-dimethyl-1,3-butadiene (**2a**) was chosen as representative. The data listed in Table 1 show that the reaction conditions profoundly influenced the outcome of this process. At 60 °C for 15 h the expected cycloadduct **3a** was never detected, neither when CH_2Cl_2, SFC, or water was used as reaction medium (Table 1, entries 4, 7, and 11) nor in the presence of a Lewis acid catalyst, such as $TiCl_4$·2THF, $AlCl_3$, or when sodium dodecyl sulfate (SDS) was added as surfactant (Table 1, entries 5, 8, 9, 12, and 13). The increase of the reaction temperature from 60 to 150 °C [7] led the uncatalyzed reactions to proceed with good yields (60−80%) (Table 1, entries 6, 10, or 14). The

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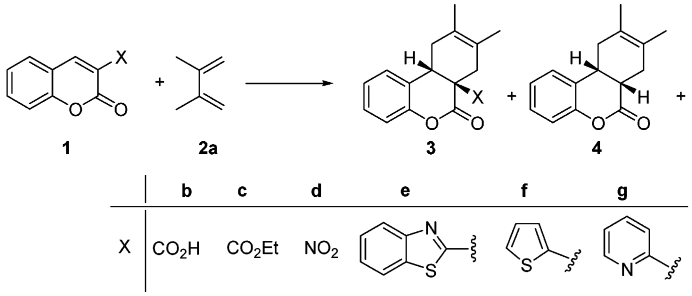
TABLE 2. Diels−Alder Reactions of Coumarins 1b−g with 2,3-Dimethyl-1,3-butadiene (2a) in Water and Under High-Pressure Condition



entry	coumarin	**2a** (equiv)	medium	*P* (kbar)	*T* (°C)	*t* (h)	product	yield (%)[a]
1	**1b**	4	H_2O		150	1	**4**/**5**[b,c]	65
2	**1b**	4	CH_2Cl_2	9	70	15	**3b**	90
3	**1c**	4	H_2O		150	3	**3c**/**4**/**5**[b,d]	75
4	**1c**	4	CH_2Cl_2	9	70	15	**3c**	90
5	**1d**	3	H_2O		90	3	**3d**	80[2c]
6	**1d**	4	CH_2Cl_2	9	30	3	**3d**	95
7	**1e**	6	H_2O		150	15	**3e**	85
8	**1e**	6	CH_2Cl_2	9	70	50	**3e**	86
9	**1f**	6	H_2O		150	15		0
10	**1f**	6	CH_2Cl_2	9	70	60	**3f**	85
11	**1g**	6	H_2O		150	15		0
12	**1g**	6	CH_2Cl_2	9	70	60	**3g**	87

[a] Yield of isolated cycloadduct. [b] The diastereoisomeric ratio was determined by GC and/or by ^{1}H NMR analyses. [c] Diastereoisomeric ratio **4**:**5** = 64:36. [d] Diastereoisomeric ratio **3c**:**4**:**5** = 77:8:15.

best yield (90%) was finally obtained when a solution of coumarin **1a** and diene **2a** in CH_2Cl_2 was treated under high pressure (9 kbar) at 60 °C for 15 h (Table 1, entry 1). Under 9 kbar pressure, the yield decreased when the reaction was carried out in THF or aqueous-THF (Table 1, entries 2 and 3). Decreasing the amount of **2a** (2 mol/equiv) or lowering the pressure to 5 kbar, the yield of **3a**, after 15 h, was only 60% and 26%, respectively.

In view of these results, we extended the study to the Diels−Alder reactions of coumarins **1b**−**g** with 2,3-dimethyl-1,3-butadiene (**2a**) in water as reaction medium and under high-pressure condition (Table 2).

In aqueous condition, the cycloadditions of **1b** and **1c** with **2a** at 150 °C occurred with good yields (65 and 75%, respectively) (Table 2, entries 1 and 3), whereas at 70 °C, only unreacted coumarins were recovered. In the case of the cycloaddition of **1b** (Table 2, entry 1), the expected cycloadduct **3b** was never isolated because, under the reaction conditions, it underwent a rapid decarboxylation reaction that led to the corresponding tetrahydro-benzochromenones **4** and **5** in a 64:36 ratio. Analogous to reports in the literature,[4e] it is foreseeable that the formation of adduct **4** and **5** occurs via (i) hydrolysis of lactonic ring of **3b**, (ii) decarboxylation of the resulting bicarboxylic acid, and (iii) intramolecular esterification to regenerate the lactone ring. Similarly, adduct **3c**, derived from the reaction between **1c** and **2a** (Table 2, entry 3) in water at 150 °C, underwent partial hydrolysis of the ester functionality with a subsequent decarboxylation to give a mixture of **3c**/**4**/**5** in a 77:8:15 ratio.

The cycloadditions of coumarins **1d** and **1e** with diene **2a** occurred in water at 90 and 150 °C, respectively (Table 2, entries 5 and 7); in these cases, the corresponding cycloadducts **3d**[2c] and **3e** were stable in the reaction conditions and could be isolated in 80% and 85% yield, respectively.

No cycloadduct was detected in the reactions of **1f** and **1g** with **2a** in water (Table 2, entries 9 and 11). Better results were obtained under high pressure. To achieve high yield (85−95%) in these conditions, 70 °C (Table 2, entries 2, 4, 8, 10, and 12) and even 30 °C (Table 2, entry 6) were adequate temperatures. When a CH_2Cl_2 solution of dienophiles **1f**, **g** and diene **2a** were placed under 9 kbar pressure at 70 °C for 60 h, high conversions were observed and cycloadducts **3f**, **g** were isolated with 85% and 87% yields, respectively (Table 2, entries 10 and 12). Furthermore, the possibility to work under milder reaction temperatures allowed the sensitive cycloadducts **3b** and **3c** to be isolated in almost quantitative yields (Table 2, entries 2 and 4).

To evaluate the regio- and *exo*/*endo*-diastereoselectivity in water and under high pressure, the Diels−Alder reaction of 3-substituted coumarins **1a** and **1b** with isoprene (**2b**) and (*E*)-piperylene (**2c)** were also examined (Scheme 2) (Table 3).

Whereas the Diels−Alder reaction of 3-phenylsulfonylcoumarin (**1a**) with isoprene (**2b**) in aqueous medium occurred in satisfactory yield at 150 °C (70%), the cycloaddition of **1a** with (*E*)-piperylene (**2c**) at the same temperature did not give the expected cycloadduct **10** (Table 3, entries 1 and 5). The Diels−Alder reactions of 3-carboxycoumarin (**1b**) with **2b** and **2c** in aqueous medium occurred at 150 °C in 65% and 85% yield, respectively, and similar to **3b**, the respective cycloadducts **9**, **15**, and **16** underwent a rapid decarboxylation reaction to chromene derivatives **7** and **8** in a 60:40 ratio and **11**/**12**/**13**/**14** in a 17:41:18:24 ratio, respectively (Table 3, entries 3 and 7).

Under high-pressure condition at 70 °C, the Diels−Alder cycloadditions of **1a** and **1b** with the 1,3-dienes **2b** and **2c** gave the corresponding cycloadducts **6**, **9**, **10** and **15**, **16**, respectively, with good yields (85%, 90%) (Table 3, entries 2, 4, 6, and 8).

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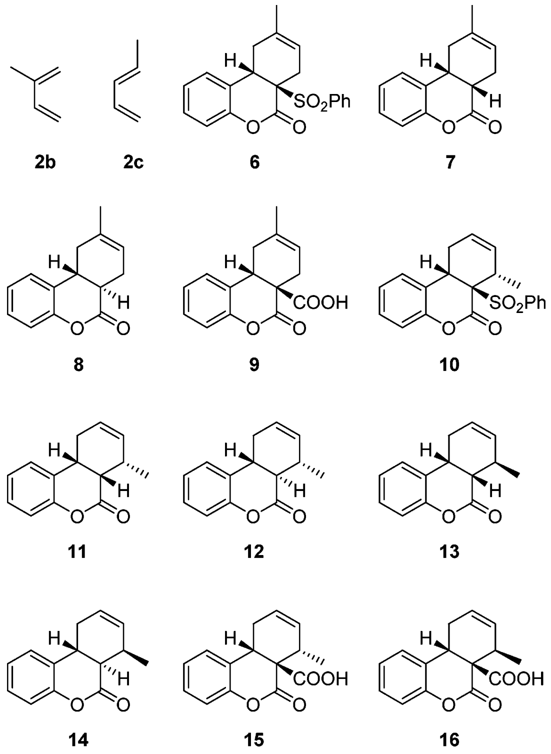
(7) The Diels−Alder cycloaddition reactions carried out in water, CH_2Cl_2, or SFC have been performed in a sealed metal reactor in which the headspace was very small. In these conditions we were not able to determine the exact internal pressure, but operating up to 150 °C it must be less than 3−4 bar. This pressure is too low to significantly influence these cycloaddition reactions; in fact, when performing the Diels−Alder reaction of 3-phenylsulfonyl coumarin (**1a**) with 2,3-dimethyl-1,3-butadiene (**2a**) at 5 kbar instead 9 kbar at 60 °C, the reaction conversion after 15 h is only 26%.

TABLE 3. Regio- and Diastereoselectivity of Diels−Alder Reactions of Coumarins 1a,b with 1,3-Dienes 2b,c in Water and under High-Pressure Condition

entry	reagents[a]	medium	*P* (kbar)	*T* (°C)	*t* (h)	product	yield (%)[b]
1	**1a**, **2b**	H_2O		150	6	**6**	70
2	**1a**, **2b**	CH_2Cl_2	9	70	20	**6**	90
3	**1b**, **2b**	H_2O		150	2	**7**/**8**[c,d]	65
4	**1b**, **2b**	CH_2Cl_2	9	70	20	**9**	90
5	**1a**, **2c**	H_2O		150	10		0
6	**1a**, **2c**	CH_2Cl_2	9	70	20	**10**	85
7	**1b**, **2c**	H_2O		150	10	**11**−**14**[c,e]	85
8	**1b**, **2c**	CH_2Cl_2	9	70	20	**15**, **16**[c,f]	90

[a] 4 equiv of 1,3-diene were used. [b] Yields of isolated cycloadducts. [c] The diastereoisomeric ratio was determined by GC and/or by ^{1}H NMR analyses. [d] Diastereoisomeric ratio **7:8** = 60:40. [e] Diastereoisomeric ratio **11:12:13:14** = 17:41:18:24. [f] Diastereoisomeric ratio **15:16** = 45:55.

SCHEME 2



The cycloadditions carried out in water or under high pressure were always totally regioselective, producing *para* adducts with isoprene (**2b**) (Table 3, entries 1−4) and *ortho* adducts with (*E*)-piperylene (**2c**) (Table 3, entries 5−8). Under high-pressure condition the Diels−Alder reaction of **1a** with **2c** was totally *endo*-diastereoselective (Table 3, entry 6) because of the steric interaction between the bulky sulfone group and the diene in the *exo* transition state,[8] whereas the cycloadditions of **1b** with **2c** gave a slight prevalence of *exo* adduct (*exo/endo* = 55:45) when carried out at 9 kbar and a prevalence of *endo* adduct (*exo/endo* = 42:58) when performed in aqueous medium (Table 3, entries 7 and 8).

Structure of Compounds. The 6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-6-ones **3a**−**c**, **3e**−**g**, **4**−**6** and **9**−**16** prepared in this work are new compounds, while adducts **7** and **8** are known compounds although only the melting points have been reported.[4e] All compounds were purified by column chromatography or by recrystallization with the exception of **11**, **14**, and **16**. All attempts to isolate these compounds in pure form were unsuccessful, and their structures were assigned by using enriched mixtures. The structures of all these compounds were inferred from the analysis of their ^{1}H and ^{13}C NMR spectra.

TABLE 4. ^3J Coupling Constant Values of Proton H(10a)

adduct	$^3J_{10a-6a}$	$^3J_{10a-10\alpha}$	$^3J_{10a-10\beta}$
4	5.5	11.0	5.5
5	10.6	13.0	5.4
7	5.0	10.9	5.9
8	11.8	12.3	5.6
11	4.7	10.8	6.3
12	14.1	10.7	5.3
13	5.0	10.3	5.5
14	14.2	10.7	5.8

The *endo*/*exo* stereochemical assignments for compounds **10**, **15**, and **16** were based on the relevant ^{1}H NMR coupling constant value, as well as on NOESY experiments. The strongly deshielded of C(7) methyl protons for compounds **10** and **15** (δ = 1.48 and 1.31 ppm, respectively) with respect to **16** (δ = 0.94), which is the consequence of the anisotropic effect of the carboxy function, indicates an *endo* configuration of the methyl group for **10** and **15** and *exo* for **16**. Support for the assigned configurations at C(7) was given by the NOESY correlations observed between H(10a) and H(7) for **10** and **15** indicating their *cis* relationship. In compound **16** the NOESY correlation observed between H(10a) and the methyl group together with the absence of a NOESY correlation between H(10a) and H(7) confirm their *trans* relationship.

The *cis*/*trans* stereochemistry at the C(6a)−C(10a) ring junction of compounds **4**, **5**, **7**, **8**, and **11**−**14** follows from the ^3J values of H(10a) (Table 4).[4c] The $^3J_{10a,10}$ values revealed a pseudoaxial H(10a) orientation with respect to the cyclohexene ring in all compounds.

While the $^3J_{10a,6a}$ values for compounds **4**, **7**, **11**, and **13** (4.7−5.5 Hz) revealed a *cis* relationship at the C(6a)−C(10a) ring junction, the same vicinal coupling constants in compounds **5**, **8**, **12**, and **14** ($^3J_{10a,6a}$ = 10.6−14.2 Hz) indicated a *trans* stereochemistry at the C(6a)−C(10a) ring junction for these compounds.

The relative *cis*/*trans* configuration between the proton H(6a) and H(7) for compounds **11**−**14** was based on the chemical shift of the C(7) methyl protons and on their coupling constant $^3J_{6a,7}$ values. The C(7) methyl protons are more deshielded in *endo* adducts **11** and **12** (δ = 1.39 and 1.28 ppm, respectively) than those in the *exo* counterparts **13** and **14** (δ = 1.16 and 1.17 ppm, respectively) presumably as a consequence of the anisotropic effect of the carbonyl function in the *endo* isomers. These results suggest a C(7) methyl group coplanar with the carbonyl function conformation for adducts **11** and **12** and consequently the configurational assignment given at C(7)-methyl for the cycloadducts **11**−**14**. Support for this assignment was also given by the comparison of the H(6a)-H(7) coupling constant values. The $^3J_{6a,7}$ for adducts **11** and **12** (13.7 and 9.4 Hz, respectively) revealed a *cis* and *trans* relationship between H(6a) and H(7), respectively, with a pseudoequatorial orientation of the methyl group at C(7) for both *endo* adducts. In contrast, the 2.6 and 4.6 Hz values observed for cycloadducts **13** and

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(8) (a) Clasby, M. C.; Craig, D.; Slawin, A. M. Z.; White, A. J. P.; Williams, D. J. *Tetrahedron* **1995**, *51*, 1509−1532. (b) Craig, D.; Fisher, D. A.; Kemal, O.; Marsh, A.; Plessner, T.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1991**, *47*, 3095−3128.

14, respectively, revealed a pseudoaxial orientation of the methyl group at C(7), confirming their *exo* configuration.

In conclusion, in water as reaction medium the Diels−Alder cycloadditions of 3-susbtituted coumarins **1a**−**e** gave satisfactory results only at 150 °C, whereas with coumarins **1f** and **1g** no reaction at all was observed. By using high pressure (9 kbar), the Diels−Alder reaction of 3-substituted coumarins **1a**−**g** with dienes **2a**−**c** allowed the corresponding cycloadducts to be prepared in excellent yields. This approach, avoids the use of any metal catalyst and makes the synthesis of a variety of 6a,7,10,10a-tetrahydro-6*H*-benzo[*c*]chromen-6-ones chemically efficient.

Experimental Section

General Procedure for Diels−Alder Reactions. The cycloaditions of **1** with **2** were accomplished (A) in water, CH_2Cl_2, and SFC and (B) under high-pressure condition. Condition A: Diene **2** (6−12 mmol) was added to 3-substituted coumarins **1** (2 mmol) dissolved in solvent (10 mL) or without solvent (SFC) in the presence of a few crystals of hydroquinone (1−2 mg)[9] in a 14- or 2-mL metal reactor, respectively. The reactor was sealed, and the resulting mixture was maintained at the indicated temperature and time,[7] then cooled and worked up as usual. Condition B: Diene **2** (4−6 mmol) and dienophile **1** (1 mmol) in the presence of a few crystals of hydroquinone were placed in a 10-mL Teflon vial that was then filled with CH_2Cl_2. The vial was closed and kept at 9 kbar at the indicated temperature and time. After depressurizing, the solvent was removed in vacuo. Each crude mixture obtained was purified by column chromatography on silica gel or by recrystallization.

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Supporting Information Available: General experimental procedures, spectral data for compounds **3a**−**g** and **4**−**16**, and the ^1H and ^{13}C NMR spectra of mixtures **11**/**14** and **15**/**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Traces of hydroquinone were added to the reagents to reduce the polymerization reaction of diene. Minuti, L.; Taticchi, A.; Gacs-Baits, E.; Marrocchi, A. *Tetrahedron* **1995**, *51*, 8953−8958.