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Hafnium Chloride Tetrahydrofuran Complex-Catalyzed Diels–Alder Cycloadditions of 3-Ethoxycarbonylcoumarins with 1,3-Dienes under Solvent-Free Conditions

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Abstract: Hafnium chloride tetrahydrofuran complex ($HfCl_4 \cdot 2\,THF$) is an efficient catalyst for the Diels–Alder cycloadditions of 3-ethoxycarbonylcoumarins **1a–c** and 1,3-butadienes **2x–z** under solvent-free conditions furnishing the corresponding cycloadducts in excellent yields. This salt is an air stable Lewis acid and therefore the reactions can be performed in air atmosphere making the procedure simple to be carried out.

Keywords: cycloaddition; Diels–Alder reaction; hafnium chloride tetrahydrofuran complex; Lewis acid catalysis; solvent-free conditions;

Coumarins are potentially versatile building blocks although, owing to their generally low reactivity, they have been scarcely investigated. The olefin of the coumarin ring is a very poor dienophile giving [4+2] cycloaddition with 2,3-dimethyl-1,3-butadiene only under severe reaction conditions and with an unsatisfactory yield.[1]

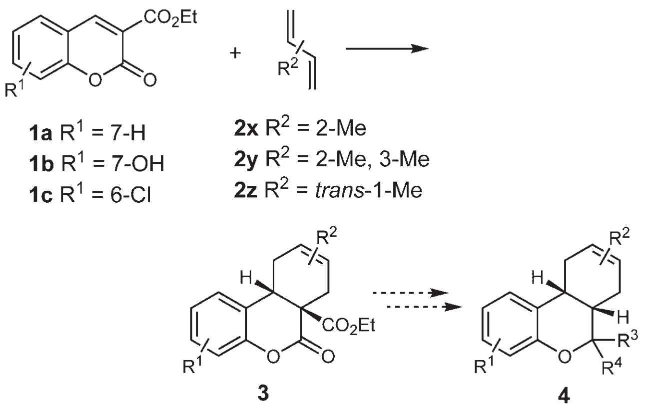
Examples of the reactivity of 3-substituted coumarins as dienophiles are rare.[2] The introduction of an alkoxycarbonyl at the C-3 position[2a–c, e] or a sulfinyl group at the C-4 position[3] slightly increases the reactivity of the 2π coumarinic system. 3-Ethoxycarbonylcoumarins underwent an ionic Diels–Alder[4] cycloaddition with 1,3-dienes in satisfactory yields upon treatment with *t*-butyldimethylsilyl triflate to form the corresponding 2-(*t*-butyldimethylsilyloxy)pyrylium salt.[2e] Activation of 3-alkoxycarbonylcoumarins by a Lewis acid was reported by using 1.2 molar equivs. of $ZnCl_2$ and a very large excess of 1,3-dienes (44 equivs.).[2c]

We have shown that 3-nitrocoumarins have satisfactory reactivity[5] and they were used as 4π components for the preparation of chromene derivatives[5b] and as 2π components for the synthesis of tetrahydrobenzo[*c*]chromenones and dihydrobenzo[*b, d*]furans[5a] in water and under solvent-free conditions (SFC). Limitations were encountered in the case of deactivated 6- and 7-hydroxy-substituted 3-nitrocoumarins.[5a]

Our research is mainly devoted to the definition of new chemically efficient and environmentally responsible synthetic procedures by using water as reaction medium[6] or SFC.[7] We have recently disclosed the $Cu(NO_3)_2$-catalyzed one-pot synthesis of optically active norstatines in water[6b] and the one-pot preparation of benzo[*e*][1,4]-oxathiepin-5-ones[7b] and of pyrido[1,2-*a*]quinoxalin-11-ium ions under SFC.[7a]

Our current project deals with the preparation of the tetrahydrobenzo[*c*]chromenone unit **3** under SFC. This moiety has a high incidence in natural products and therefore is included in the set of “privileged structures”.[8] Among all the biologically active compounds possessing the benzopyran template,[8] we are interested in the synthesis of cannabinoids **4** through a new synthetic approach based on the Diels–Alder cycloaddition of 3-ethoxycarbonylcoumarins **1** with 1,3-butadienes **2**, under SFC, and subsequent manipulation of the corresponding tetrahydrobenzo[*c*]chromenone **3** (Scheme 1).

Considering that 3-ethoxycarbonylcoumarins **1** require a significant activation to react as dienophiles with electron-rich 1,3-dienes, we have planned to reach this goal by combining the use of a Lewis acid and SFC. In fact in the absence of reaction medium the reactions are generally faster and give higher selectivities and yields; in addition, they require simpler equipments and work-up procedures are usually easier.[7,9,10] In this paper we report the results obtained in the reactions of



Scheme 1.

3-ethoxycarbonylcoumarins **1a**–**c** with 1,3-dienes **2x**–**z** in the presence of a variety of Lewis acid catalysts under SFC and in comparison with different reaction media.

Considering that metal triflates are proving to be very efficient Lewis acid catalysts for fundamental organic processes[11,12] and that, in our hands, under SFC $In(OTf)_3$ was a more efficient catalyst for the thiolysis of 1,2-epoxides than other In(III) salts,[13] we have initially studied the cycloaddition reaction of the representative 3-ethoxycarbonylcoumarin (**1a**) and isoprene (**2x**) under SFC at 30 °C in the presence and absence of various triflate catalysts [Zn(II), Cu(II), Yb(III), In(III), Hf(IV), and Al(III)]. To compare the efficiency of this pool of catalysts, we have also included in our study two chloride salts such as $TiCl_4$ and $HfCl_4$ and their THF complexes, $TiCl_4 \cdot 2\,THF$ and $HfCl_4 \cdot 2\,THF$. All the results are illustrated in Table 1.

With the exception of $Al(OTf)_3$ all the triflates considered in this study have been already used to catalyze the Diels–Alder cycloaddition in organic solvents.[14] Although their catalytic efficiency has been scarcely investigated, $HfCl_4$ and $Hf(OTf)_4$ have recently proved to be very efficient oxophilic Lewis acids promoting a number of useful transformations[12] including Diels–Alder cycloadditions.[12a, b] To our knowledge $HfCl_4 \cdot 2\,THF$ has never been used as catalyst for this transformation.

Table 1. Lewis acid-catalyzed cycloaddition of **1a** with isoprene (**2x**).[a]

Entry	Lewis acid (5 mol %)	Conversion[b]
1	None	32[c]
2	None	12[c, d]
3	$Zn(OTf)_2$	Traces
4	$Cu(OTf)_2$	Traces
5	$Yb(OTf)_3$	Traces
6	$In(OTf)_3$	12
7	$Hf(OTf)_4$	25
8	$Al(OTf)_3$	95
9	$TiCl_4 \cdot 2\,THF$	traces[e]
10	$TiCl_4$	–
11	$HfCl_4$	24
12	$HfCl_4 \cdot 2\,THF$	98[f]

[a] 4 molar equivs., 30 °C, 6 h.
[b] Conversion to adduct **3ax** determined by GLC analyses.
[c] Reaction performed at 140 °C.
[d] Reaction performed in toluene.
[e] Complete conversion was reached after 24 h by using 25 mol % of $TiCl_4 \cdot 2\,THF$.
[f] Adduct **3ax** was isolated in 95% yield.

Although in the absence of the catalyst the conversion of **1a** to adduct **3ax** was low also at 140 °C, it can be concluded that SFC promoted the cycloaddition if compared to the results obtained in toluene (Table 1, entry 1 *vs.* 2). $Zn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$, $Hf(OTf)_4$ and $HfCl_4$ gave at 30 °C after 6 h only traces or very low conversions to **3ax** (Table 1, entries 3–7, and 11). $TiCl_4$ did not work at all while 25 mol % of $TiCl_4 \cdot 2\,THF$ allowed a complete conversion to be reached after 24 h (Table 1, entries 9 and 10, see footnote [e]).

Excellent conversions were obtained by using $Al(OTf)_3$ and $HfCl_4 \cdot 2\,THF$ (Table 1, entry 8 and 12) with a slightly better result for the latter which gave a very clean reaction mixture and allowed the adduct **3ax** to be isolated in 95% yield.

The higher catalytic efficiency of $Al(OTf)_3$ and $HfCl_4 \cdot 2\,THF$ can be ascribed to their higher ability to coordinate both the carbonyl oxygens of the ester and lactone functionalities of **1** with the formation of the corresponding pyrylium cation (**A**, Figure 1) which is strongly activated towards the normal electron demand cationic Diels–Alder reaction.[4a] To the best of our knowledge the significantly better catalytic properties of $HfCl_4 \cdot 2\,THF$ *vs.* $HfCl_4$ in the carbo-Diels–Alder reaction have never been noticed.

We have chosen $HfCl_4 \cdot 2\,THF$ to continue our investigations considering that this THF-complex salt is a very convenient and easy to handle Hf(IV) source, in fact it is an air-stable solid which melts at 187 °C.

In addition, we compared the catalytic efficiency of $HfCl_4 \cdot 2\,THF$ the use of various reaction media was

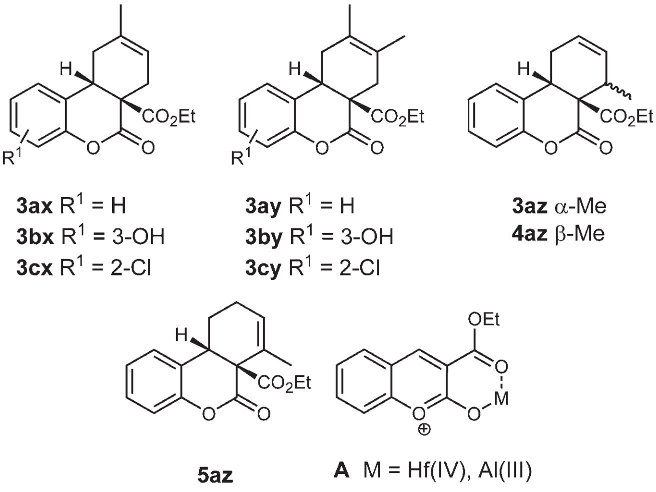


Figure 1.

Table 2. $HfCl_4 \cdot 2$ THF-catalyzed cycloaddition of **1a** with **2x** in various reaction media at 30 °C.[a]

Entry	Reaction Medium	Conversion[b]
1	SFC	98
2	CH_3NO_2	50
3	CH_2Cl_2	40
4	CH_3CN	10
5	MeOH	5[c]
6	THF	2
7	H_2O (pH 1.6)	–
8	[bmim]PF_6	35

[a] 0.05 molar equivs. of $HfCl_4 \cdot 2$ THF, 4 equivs. of **2x**.

[b] Conversion to adduct **3ax** determined by GCL analyses after 6 h reaction time.

[c] 43% of the corresponding methyl ester of **1a**.

also considered and compared with SFC, the results are illustrated in Table 2. Among the organic media nitromethane, as expected, was the best organic solvent giving after 6 h at 30 °C 50% conversion of **1a** to **3ax** (Table 2, entry 2). Slightly lower conversions were obtained in CH_2Cl_2 and in the ionic liquid [bmim]PF_6 (Table 2, entries 3 and 8), while very low conversions to adduct **3ax** were reached in strongly complexing media such as CH_3CN, MeOH, THF, and water (Table 2, entries 4–7). In conclusion the Diels–Alder reaction of **1a** with **2x** gave the best result when it was carried out under SFC and in the presence of 0.05 equivs. of $HfCl_4 \cdot 2$ THF at 30 °C for 6 h.

The protocol was then extended to the cycloadditions of **1a** with 2,3-dimethyl-1,3-butadiene (**2y**) and (*E*)-piperylene (**2z**) and to those of 7-hydroxy-3-ethoxycarbonylcoumarin (**1b**) and 6-chloro-3-ethoxycarbonylcoumarin (**1c**) with **2x** and **2y**. The Diels–Alder reaction of **1a** and **2y** is very fast and gave a quantitative conversion at 30 °C in 4 h (Table 3, entry 1) . To complete the reaction of **1a** with the poorly reactive **2z** 0.25 equivs. of catalyst were necessary at 50 °C and a mixture of *ortho* adducts **3az** (*endo*):**4az** (*exo*):**5az** in a 17:26:57 ratio was obtained in 92% overall yield (Table 3, entry 2). Compound **5az** is formed upon double bond migration from **3az** and **4az** as already observed.[5a] By performing the same reaction in nitromethane the yield was lower but the composition of the reaction mixture was identical (Table 3, entry 3). The diasteroselectivity of the reaction reflects a balance between steric interactions and electronic effects.

The coumarin **1b** is poorly reactive due to the presence of a hydroxy group,[5a] nevertheless, by using 0.25 molar equivs. of $HfCl_4 \cdot 2$ THF, adducts **3bx** and **3by** were obtained in good yields (Table 3, entries 4 and 5). 6-Chloro-3-ethoxycarbonylcoumarin (**1c**) reacted rapidly at 30 °C with both **2x** and **2y** giving the corresponding adducts **3cx** and **3cy** in almost quantitative yields (Table 3, entries 6 and 7).

In conclusion, we have found that under SFC, $HfCl_4 \cdot 2$ THF is a very efficient Lewis acid for Diels–Alder cycloadditions of 3-ethoxycarbonylcoumarins **1a–c** with 1,3-butadienes **2x–z**,[15] allowing the corresponding cycloadducts to be prepared in excellent yields. This result opens, for the first time, a chemically efficient and environmentally safe general route to access tetrahydrobenzo[*c*]chromene derivatives.

Experimental Section

Typical Procedure for the $HfCl_4 \cdot 2$ THF-Catalyzed Diels–Alder Cycloaddition

A screw-capped vial equipped with a magnetic stirrer was charged with $HfCl_4 \cdot 2$ THF, (0.05 mmol, 0.023 g) and 3-ethoxycarbonylcoumarin (**1a**; 1.0 mmol, 0.218 g), then isoprene (**2x**; 4.0 mmol, 0.272 g) was added The resulting mixture was left under magnetic stirring at 30 °C for 6 h. After silica-gel column chromatography of the final mixture (EtOAc/petroleum ether, 2/8 gradient) cycloadduct **3ax** was isolated; yield: 0.272 g (95%).

Helped by our previous experience with similar compounds,[5a] all the structures of the cycloadducts have been confirmed by the spectroscopic data. In the case of 4az, which has been isolated as a pure compound, NOESY correlations between Me and H-10a and between Me and H-1 confirmed the *exo* structure.

Table 3. $HfCl_4 \cdot 2$ THF-catalyzed cycloaddition of **1a–c** with **2x–z** under SFC at 30 °C.

Entry	Coumarin	1,3-Diene (equivs.)	$HfCl_4 \cdot 2$ THF (equivs.)	*t* (h)	Products	Yield[a]
1	**1a**	**2y** (4)	0.05	4	**3ay**	95
2	**1a**	**2z** (7)	0.25	15	**3az** : **4az** : **5az**	92[b, c]
3	**1a**	**2z** (7)	0.25	15	**3az** : **4az** : **5az**	60[b, d]
4	**1b**	**2x** (7)	0.25	30	**3bx**	75[b]
5	**1b**	**2y** (7)	0.25	30	**3by**	82
6	**1c**	**2x** (4)	0.05	6	**3cx**	90
7	**1c**	**2y** (4)	0.05	4	**3cy**	92

[a] Yield of isolated products after purification on silica gel column chromatography.

[b] Reaction performed at 50 °C.

[c] Adducts ratio 17:26:57, respectively.

[d] Nitromethane as reaction medium, adducts ratio 21:24:55.

Full characterization charts (^{1}H NMR, ^{13}C NMR, IR, GC-MS, R_f) for compounds **1b**, **1c**, **3ax–z**, **3bx–y**, **4az**, **5az** are available in the Supporting Information.

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[14] For an overview of Lewis acid-catalyzed Diels–Alder reactions see refs.[4a, b] for some examples regarding $Zn(OTf)_2$, $Cu(OTf)_2$, $Yb(OTf)_3$, see: *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**; for $In(OTf)_3$, see: F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *Curr. Org. Chem.* **2003**, *7*, 1661–1689; for $Hf(OTf)_4$ see refs.[12a, b]

[15] $HfCl_4 \cdot 2\,THF$ proved to be a very efficient catalyst for the Diels–Alder reaction of various α,β-unsaturated carbonyl compounds. For example, by using the protocol reported in this paper, ethyl acrylate, 3-hepten-2-one, and 3-acryloyl-1,3-oxazolidin-2-one reacted with 2,3-dimethyl-1,3-butadiene at 50 °C in 15, 12, and 0.5 h, respectively, giving almost complete conversions to the corresponding cycloadducts.