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The Synthesis of Substituted Benzo[*c*]chromen-6-ones by a Suzuki Coupling and Lactonization Sequence Using Ionic Liquids – from Laboratory Scale to Multi-Kilogram Synthesis

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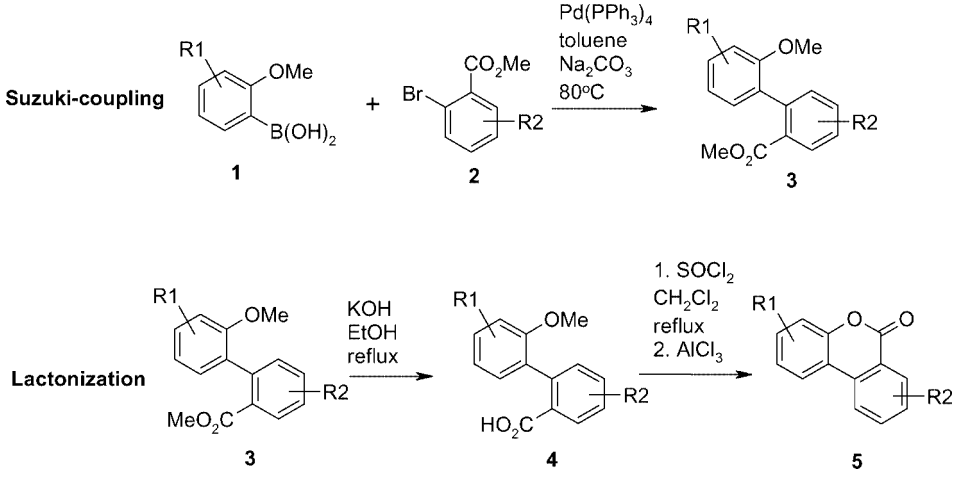
A series of benzo[*c*]chromen-6-ones are prepared by a Suzuki coupling and lactonization sequence starting with 2-methoxyphenylboronic acids and methyl 2-bromobenzoate derivatives. The use of ionic liquids in this synthesis has been explored. It was found that the Suzuki coupling proceeds much faster when a catalytic amount of the ionic liquid [BMIM][PF_6] is used. By using the Lewis acidic ionic liquids [BMIM][Al_2Cl_7] or [TMAH][Al_2Cl_7] the methyl 2-(2-methoxyphenyl)benzoate product obtained from the Suzuki coupling can be converted to benzo[*c*]chromen-6-ones in one step, while the conventional route involves three steps. The use of ionic liquids is demonstrated in the synthesis of a variety of benzo[*c*]chromen-6-ones. It is also shown that the application of ionic liquids is not limited to laboratory scale experiments, as a process was developed and performed on a multi-kilogram scale.

Introduction

The use of ionic liquids in organic synthesis has been extensively described and reviewed during the past decade.[1] There are several examples in which ionic liquids have a surprising effect on chemical reactions performed in these solvents. It has been demonstrated that ionic liquids profoundly influence the rate of palladium-catalyzed reactions.[2–5] Also Diels–Alder reactions,[6] Friedel–Crafts reactions[7] and nucleophilic substitutions[8] display deviating behavior when conducted in these contemporary solvents. This paper deals with the use of ionic liquids in the synthesis of the substituted benzo[*c*]chromen-6-ones **5**. The benzo[*c*]chromen-6-one structure recurs in the synthesis of various pharmaceutically interesting compounds that potentially find application as progesterone,[9] glucocorticoid,[10] and androgen receptor ligands.[11] The synthesis of the benzo[*c*]chromen-6-one structure generally starts with a



Scheme 1.

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Suzuki coupling of a 2-methoxyphenylboronic acid **1** and a methyl 2-bromobenzoate **2** followed by a lactonization sequence. This synthesis, which is shown in Scheme 1, allows many functional groups in both aromatic blocks.

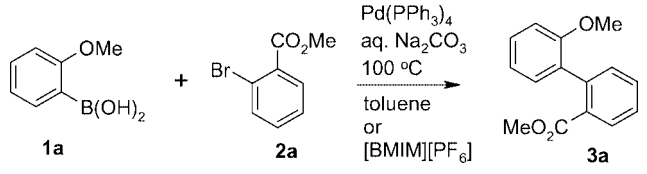
For both the Suzuki coupling and the lactonization sequence, alternatives employing ionic liquids can be envisaged. Firstly, the Suzuki coupling reaction has been described in ionic liquids.[5] This paper details an investigation of the effect of ionic liquids on the Suzuki coupling of 2-methoxyphenylboronic acid and methyl 2-bromobenzoate. This study sheds light on the effect of the palladium source and phosphane ligands in organic solvents and ionic liquids. Also the possibility of recycling of catalyst and the ionic liquid is elucidated.

Secondly, shorter alternatives for the three-step lactonization sequence depicted in Scheme 1 have been elaborated. The advantages of the benzo[*c*]chromen-6-one synthesis mediated by ionic liquids are demonstrated for a series of compounds bearing a variety of functional groups. Furthermore, the present study was aimed at the development of an up scalable process for the preparation benzo[*c*]chromen-6-ones. Lastly, the feasibility of ionic-liquid technology on multi-kilogram scale has been demonstrated.

Results

Suzuki Coupling of 2-Methoxyphenylboronic Acid and Methyl 2-Bromobenzoate in Toluene and [BMIM][PF_6]

The paper of Welton et al.[5] has been used as a starting point for our investigation. The conditions employed in this paper for the Suzuki coupling of bromobenzene and phenylboronic acid were also applied for the coupling of 2-methoxyphenylboronic acid and methyl 2-bromobenzoate (Scheme 2), viz. using $Pd(PPh_3)_4$ as the catalyst and aqueous Na_2CO_3 and ionic liquid as a biphasic medium at 100 °C. Instead of the water-miscible [BMIM][BF_4], we used the water-immiscible ionic liquid [BMIM][PF_6] to allow for easier separation of the ionic liquid from the water layer. The reaction was also conducted under the same conditions in toluene.



Scheme 2.

The Suzuki coupling in [BMIM][PF_6] was completed after 30 minutes reaction time. After cooling the reaction mixture the aqueous layer was separated from the ionic liquid. The ionic liquid was extracted five times with toluene, after which virtually no more product was extracted. The ionic liquid containing the catalyst was washed twice with water to remove salts and was reused subsequently. The latter was not possible for reactions carried out in toluene, as during work up of these reactions the catalyst was not recoverable. The results of the reactions in toluene and [BMIM][PF_6], respectively, as well as the results with the recycled ionic liquid/catalyst solution are shown in Table 1. It should be mentioned that the reaction in toluene (Entry 1) and the first three cycles in ionic liquid (Entry 2–4) ran to complete conversion, while during the fourth and fifth recycle (Entry 5–6) the reaction was not completed even after 22 hours.

Table 1. Suzuki coupling of **1a** and **2a** in [BMIM][PF_6] and toluene.

Entry	Solvent	Cycle	Reaction time [h]	Isolated yield [%]
1	toluene	n.a.	30	99
2	[BMIM][PF_6]	1	0.5	75
3	[BMIM][PF_6]	2	20	91
4	[BMIM][PF_6]	3	20	68
5	[BMIM][PF_6]	4	22+	43
6	[BMIM][PF_6]	5	22+	10

Clearly, the rate of the reaction in ionic liquids decreased after each recycle of the ionic liquid/catalyst system. The first three cycles (Entry 2–4) the reaction time was shorter than in toluene, but the average yield was lower in ionic liquids. Remarkably, the yield of the second cycle (Entry 3) is higher than that of the first cycle although both reactions ran to complete conversion. This poor reproducibility is attributed to the difficult extraction of product from the ionic liquid layer. The deterioration of the catalyst/ionic liquid system can be explained by catalyst leaking from the ionic liquid during the extensive toluene washings required to extract the product from the ionic liquid. The recycling experiment described in Scheme 2 and Table 1, was repeated using $Pd(OAc)_2$ and Pd/C as palladium sources in combination with triphenylphosphane. These series showed the same deteriorating results as those in Table 1. In summary, the ionic liquid has a beneficial effect on the kinetics of the Suzuki coupling reaction as concluded from comparing Entries 1 and 2. However, because of the difficult extraction of product from the ionic liquid, the isolated yield from the reaction in toluene is higher than that in [BMIM][PF_6]. Furthermore, reuse of the [BMIM][PF_6]/catalyst system in a reproducible manner appeared not feasible.

In view of these results it was investigated whether the beneficial effect of ionic liquids on the reaction rate, and the easy work up using toluene as a solvent could be combined. To this end, a series of reactions were performed with 1.2 mol-% of catalyst in toluene either with or without 4.8 mol-% of [BMIM][PF_6]. The ratio of Pd/[BMIM][PF_6] of 1:4 was chosen assuming that the ionic liquid may serve as a ligand to the palladium catalyst in which case four equivalents would be required if all phosphane ligands were to be displaced. No efforts have been put in reducing this amount of [BMIM][PF_6]. As catalysts $Pd(PPh_3)_4$, as well as $Pd(OAc)_2$ and Pd/C in combination with PPh_3 were subjected. The results are shown in Table 2.

The results in Table 2 reveal that for the three palladium sources used, viz. $Pd(PPh_3)_4$, $Pd(OAc)_2$, and Pd/C, the catalyst activity is enhanced by the presence of 4.8 mol-% of

Table 2. The effect of a catalytic amount of [BMIM][PF_6] on the Suzuki coupling reaction.

Catalyst[a]	[BMIM][PF_6][b]	Yield [%]	Reaction time [h]
$Pd(PPh_3)_4$	N	99	30
$Pd(PPh_3)_4$	Y	90	0.5
$Pd(OAc)_2$, PPh_3[b]	N	88	30
$Pd(OAc)_2$, PPh_3[b]	Y	90	3.5
Pd/C, PPh_3[b]	N	94	22
Pd/C, PPh_3[b]	Y	90	8

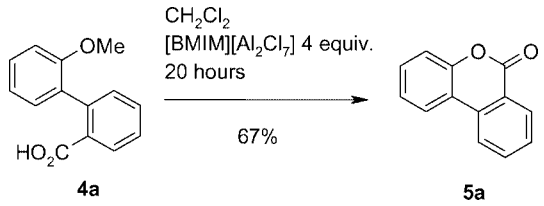
[a] 1.2 mol-% of palladium. [b] 4.8 mol-%.

[BMIM][PF_6]. The reaction rate is up to a factor 10 higher when a catalytic amount of [BMIM][PF_6] is added to the reaction mixture. Interestingly, only the kinetics is positively influenced by the presence of [BMIM][PF_6], while the yields are about the same. This is in contrast to the experiments with [BMIM][PF_6] as a solvent, as with those conditions extraction problems caused a significant decrease of the isolated product yield. The reactions were repeated with 4.8 mol-% of the salt [BMIM]Cl, which is the precursor of the ionic liquid [BMIM][PF_6]. In the presence of [BMIM]Cl virtually identical results were observed. A plausible explanation for the effect of the [BMIM] cation is that imidazolium carbene species are formed through deprotonation in the basic medium. It has been reported that imidazolium carbenes are excellent ligands for palladium catalysts.[12] The enhancement of the catalyst activity resulting in a 10-fold shorter reaction time presents notable example of process intensification by ionic liquids.

Lactonization of Methyl 2-(2-Methoxyphenyl)benzoate (3a) to Benzo[*c*]chromen-6-one (5a) Using Lewis Acidic Chloroaluminate Ionic Liquids

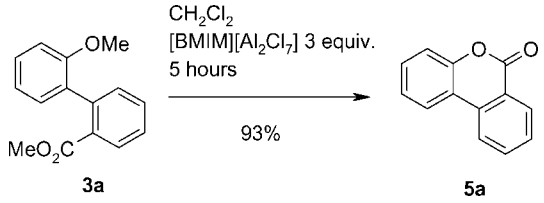
The lactonization of **3** to **5** by the process described in Scheme 1 involves three subsequent steps. First the ester is saponified. The thus obtained acid **4a** is converted into its acid chloride by reaction with thionyl chloride and subsequently treated with aluminum chloride giving the lactone **5**. Although this sequence proceeds in high yield, it is a rather elaborate process that requires a large amount of organic solvents in the consecutive steps and work up procedures. In addition, the use of thionyl chloride is not preferred on industrial scale.

The lactonization in Scheme 1 includes an aromatic ether cleavage. As chloroaluminate-based ionic liquids have proven to be particularly useful in aromatic ether cleavage,[13] their application in the lactonization of **3** can be envisaged. Our first objective was to avoid the use of thionyl chloride for the activation of carboxylic acid **4a** by treating the acid with the Lewis acidic ionic liquid [BMIM][Al_2Cl_7] (Scheme 3). To our satisfaction, the lactonization of the carboxylic acid by [BMIM][Al_2Cl_7] was achieved, and the product was isolated in a yield of 67%. Because in-process analysis showed complete conversion of **4a** to **5a**, it is suspected that the relatively low yield of 67% can be attributed to product losses during work up. When carboxylic acid **4a** was treated with aluminum chloride, no trace of **5a** could be detected, which points at a difference in reactivity between aluminum chloride and [BMIM][Al_2Cl_7].



Scheme 3. Lactonization of **4a** by [BMIM][Al_2Cl_7].

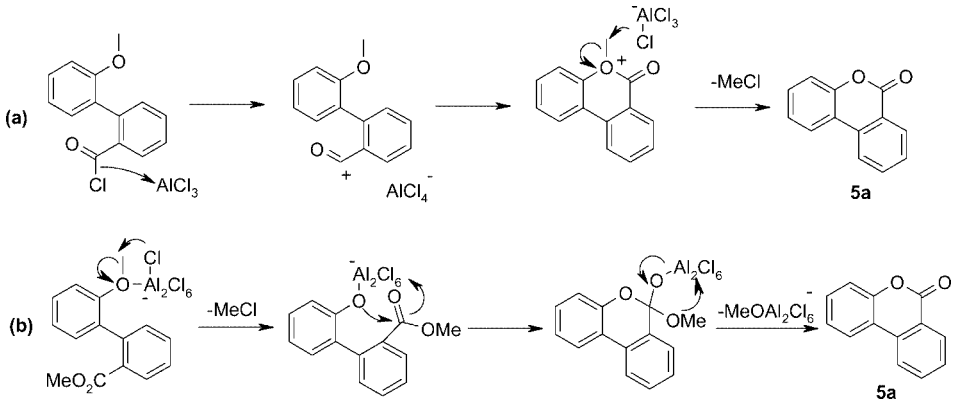
In a further attempt to shorten the three-step process for the conversion of **3a** into **5a**, the ester **3a** was subjected to the same conditions (Scheme 4). Astonishingly, the ester **3a** was readily converted to the lactone **5a** when treated with 3 equiv. of [BMIM][Al_2Cl_7] in dichloromethane. The lactone was obtained after work up in a yield of 93%. Although the yield is comparable to that of the three-step procedure described in Scheme 1, viz. 91%, the ionic liquid-mediated lactonization is much faster and less elaborate, and features a perfect example of process intensification. Despite the fact that the ionic liquid needs to be destructed by aqueous work up of the reaction, resulting in the formation of aluminate salts as a waste product, the environmental impact is tremendously reduced by using less organic solvents and avoiding reagents such as thionyl chloride.



Scheme 4. Lactonization of ester **3a** with [BMIM][Al_2Cl_7].

It should be noted that upon treatment of the ester **3a** with three equiv. of aluminum chloride, we observed a much slower reaction leading to incomplete conversion to **5a** after 48 hours, while the reaction with three equiv. of [BMIM][Al_2Cl_7] was completed within 5 hours.

The differences observed between the effectiveness of aluminum chloride and [BMIM][Al_2Cl_7] in the lactonization of the ester **3a** and acid **4a**, led to the following mechanistic considerations. Lactonization via the acid chloride most likely proceeds by acylative ether cleavage (Scheme 5 route a).[14] In this mechanism, reaction of the acid chloride with aluminum chloride leads to an acylium ion that coordinates with the oxygen atom of the methoxy function. Subsequent attack of a chloride ion to the methoxide carbon cleaves the methyl ether bond and liberates the lactone and chloromethane. As acylium-ion formation from a carboxylic acid or ester is much more cumbersome than from acid chlorides, the lactonization of the ester **3a** is deemed to proceed through another mechanism as de-



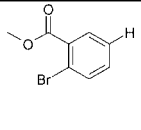
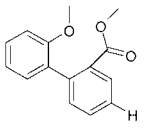
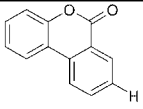
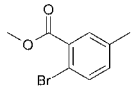
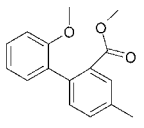
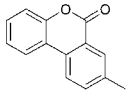
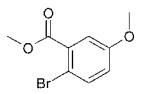
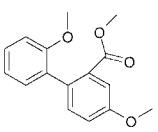
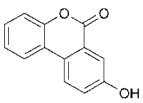
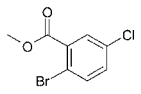
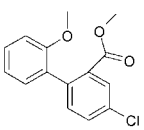
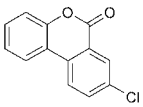
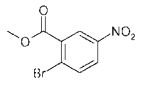
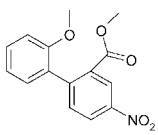
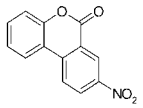
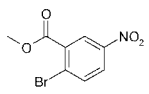
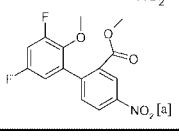
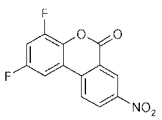
Scheme 5. Tentative mechanism of lactonization via the acid chloride (route a) and via the ester (route b).

picted in Scheme 5, route b. In this mechanism, the methyl ether is cleaved, and the thus formed phenoxide-aluminate complex subsequently undergoes lactonization. It has been reported that chloroaluminate ionic liquids are highly active ether-cleaving agents that are superior to their conventional counterpart aluminum chloride.[13] This supports route b in Scheme 5 as for the conversion of **3a** or **4a** into the lactone **5a**, aluminum chloride was not reactive, respectively less reactive, than [BMIM][Al_2Cl_7].

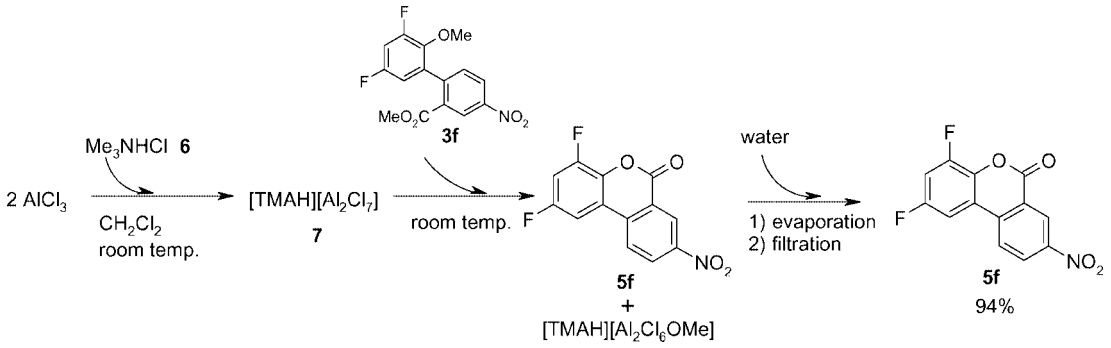
The Synthesis of a Variety of Substituted Benzo[*c*]chromen-6-ones

After having developed the two-step synthesis for benzo[*c*]chromen-6-one (**5a**) employing ionic liquids, the scope of this methodology was explored. To this end several substituted phenylboronates and methyl bromobenzoates were used to prepare the corresponding benzo[*c*]chromen-6-ones. The results are shown in Table 3.

Table 3. The results of the synthesis of substituted benzo[*c*]chromen-6-ones **5a**–**f**.

	Methyl 2-bromobenzoat **1**	Suzuki product **3**	Yield (%)	Lactonization product **5**	Yield (%)	Overall (%)
a			99		93	92
b			98		98	96
c			86		59	51
d			71		70	50
e			68		93	63
f		 [a]	88		98	86

[a] For the synthesis of **3f** 3,5-difluoro-2-methoxyphenylboronic acid was used.



Scheme 6. Large-scale process for the conversion of **3f** into **5f**.

As is evident from Table 3, the developed methodology can be used for the synthesis of a variety of substituted benzo[*c*]chromen-6-ones. All Entries provide the product in only two steps in good overall yield. The methodology allows both electron-withdrawing and electron-releasing groups to be present at either of the aromatic rings. Entry c did not furnish the expected methoxy derivative but the hydroxy derivative **5c** instead. We have reported before, that Lewis acidic ionic liquids are excellent ether cleaving agents.[13] The conversion of **3c** into **5c**, involves two reactions, viz. lactonization and methyl-ether cleavage, which proceed in an overall yield of 59%.

To demonstrate the feasibility of industrial application of the developed methodology, the lactonization process was also studied using the Lewis acidic ionic liquid derived from trimethylamine hydrochloride and aluminum chloride instead of [BMIM][Al_2Cl_7]. Trimethylamine hydrochloride is much cheaper than 3-butyl-1-methyl-imidazolium chloride ([BMIM]Cl) and is readily available in bulk. By using [TMAH][Al_2Cl_7] an up scalable process for the conversion of **3f** into **5f** was developed. This process is outlined in Scheme 6. To a suspension of aluminum chloride, trimethylamine hydrochloride was added in portions. In this way, the exothermicity of the reaction can be controlled excellently. To the thus prepared solution of the ionic liquid **7**, the starting material **3f** was added. After completion of the reaction, water was added to quench the chloroaluminate ionic liquid and to dissolve the resulting aluminate and amine salts. The product precipitated and was filtered off after the removal of dichloromethane by distillation. The process shown in Scheme 6 has been performed in our Kilolab facility four times on 7-kg scale. This example demonstrates that the developed methodology not only serves as an efficient synthesis for benzo[*c*]chromen-6-ones on laboratory-scale, but is feasible on multi-kilogram scale as well.

Conclusions

The Suzuki coupling of 2-methoxyphenylboronic acids **1** and methyl 2-bromobenzoates **2** proceeds much faster in imidazolium-based ionic liquids compared with toluene. However, the poor extractability of the products from the ionic liquid resulted in a low yield when reactions were conducted in ionic liquids. The advantage of the ionic liquid, viz. catalyst enhancement, and the advantage of toluene as a solvent, viz. easy work up, were efficiently combined by using 4.8 mol-% of [BMIM][PF_6] or its precursor [BMIM]-Cl in the reaction in toluene. In this way, the ionic liquid enhanced the rate of the reaction by a factor ten and the easy work up furnished the products in excellent yields.

The methyl 2-(2-methoxyphenyl)benzoates **3** formed could be converted into benzo[*c*]chromen-6-ones **5** in one step by treatment with a Lewis acidic chloroaluminate ionic liquid. This procedure proved much more efficient than the three-step sequence that was deployed originally. In addition, by using the one-step ionic liquid-mediated reaction, the amount of organic solvents used decreased significantly, and the use of thionyl chloride could be avoided. By using a low-cost ionic liquid prepared from trimethylamine hydrochloride and aluminum chloride, the lactonization process was developed and scaled up to 7-kg scale. This demonstrates the industrial feasibility of this process using ionic liquids.

The results described in this paper show how the application of water-stable and Lewis acidic ionic liquids can be used for process intensification, reducing both reaction time and waste of reagents and organic solvents.

Experimental Section

General Remarks: Reactions were monitored with a HP 6890 Series GC and TLC (silica gel). The NMR spectra were recorded with a Bruker DPX-400. Mass spectroscopy was performed with a PE Sciex API 165.

Methyl 2-(2-Methoxyphenyl)benzoate (3a): A mixture of *o*-methoxyphenylborate (0.78 g, 5.1 mmol), methyl *o*-bromobenzoate (0.653 mL, 4.7 mmol), Na_2CO_3 (1.05 g, 9.9 mmol), $Pd(OAc)_2$ (12.7 mg, 1.2 mol-%), triphenylphosphane (59 mg, 4.8 mol-%), and [BMIM][Cl] (20 mg, 4.8 mol-%) in water (3 mL) and toluene (7 mL) was heated to reflux temperature. The progress of the reaction was monitored by TLC (silica gel, ethyl acetate/heptane, 1:3). The reaction was completed after 3.5 hours. The toluene layer was separated, and the water layer was extracted twice with toluene (7 mL). The combined toluene fraction was washed with an aqueous $NaHCO_3$ solution and with brine. The toluene was dried with $MgSO_4$ and the solvents evaporated to dryness. Yield 1.13 g (99%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (dd, 1 H), 7.54 (t, 1 H), 7.39 (t, 1 H), 7.30–7.36 (m, 2 H), 7.25 (dd, 1 H), 7.04 (t, 1 H), 6.91 (d, 1 H), 3.72 (s, 3 H), 3.65 (s, 3 H) ppm.

Methyl 2-(2-Methoxyphenyl)-5-methylbenzoate (3b): The procedure was the same as for **3a**. Yield: 1.18 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (s, 1 H), 7.29–7.37 (m, 2 H), 7.21–7.25 (m, 2 H), 7.02 (t, 1 H), 6.88 (d, 1 H), 3.71 (s, 3 H), 3.64 (s, 3 H), 2.41 (s, 3 H) ppm.

Methyl 2-(2-Methoxyphenyl)-5-methoxybenzoate (3c): The procedure was the same as for **3a**. Yield: 1.10 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, 1 H), 7.31 (t, 1 H), 7.21–7.27 (m, 2 H), 7.08 (dd, 1 H), 7.02 (t, 1 H), 6.88 (d, 1 H), 3.87 (s, 3 H), 3.72 (s, 3 H), 3.64 (s, 3 H) ppm.

Methyl 5-Chloro-2-(2-methoxyphenyl)benzoate (3d): The procedure was the same as for **3a**. Yield: 0.921 g (71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, 1 H), 7.51 (dd, 1 H), 7.34 (t, 1 H), 7.27 (d, 1 H), 7.21 (d, 1 H), 7.03 (t, 1 H), 6.90 (d, 1 H), 3.72 (s, 3 H), 3.66 (s, 3 H)

Methyl 2-(2-Methoxyphenyl)-5-nitrobenzoate (3e): The procedure was the same as for **3a**. Yield: 0.885 g (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (d, 1 H), 8.37 (dd, 1 H), 7.53 (d, 1 H), 7.41 (t, 1 H), 7.26 (dd, 1 H), 7.08 (t, 1 H), 6.94 (d, 1 H), 3.74 (s, 6 H) ppm.

Methyl 2-(3,5-Difluoro-2-methoxyphenyl)-5-nitrobenzoate (3f): The procedure was the same as for **3a**. Yield: 382 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (d, 1 H), 8.41 (dd, 1 H), 7.52 (d, 1 H), 6.94 (m, 1 H), 6.77 (m, 1 H), 3.81 (s, 3 H), 3.63 (s, 3 H) ppm.

Benzo[*c*]chromen-6-one (5a): Methyl 2-(2-methoxyphenyl)benzoate (**3a**) (1.00 g, 4.1 mmol) was dissolved in dichloromethane (20 mL). To this solution, [BMIM][Al_2Cl_7] (4.6 mL, 12.3 mmol) was added. Then the reaction mixture was heated to reflux. After 20 hours the reaction was completed (TLC, silica gel/toluene) and the reaction mixture was cooled to room temperature. The reaction mixture was poured into ice water and the dichloromethane was separated and the water layer was extracted three times with dichloromethane. The combined dichloromethane layers were washed with saturated $NaHCO_3$ solution and water. Then the organic layer was dried with $MgSO_4$ and the solvents evaporated. Yield: 0.801 g of **5a** (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (dd, 1 H), 8.14 (d, 1 H), 8.08 (dd, 1 H), 7.83 (t, 1 H), 7.60 (t, 1 H), 7.50 (t, 1 H), 7.34–7.39 (m, 2 H) ppm. This compound has been reported in the literature.[15]

8-Methylbenzo[*c*]chromen-6-one (5b): The procedure was the same as for **5a**. Yield: 0.947 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 8.01–8.06 (m, 2 H), 7.65 (d, 1 H), 7.46 (t, 1 H), 7.31–7.37 (m, 2 H), 2.50 (s, 3 H) ppm. This compound has been reported in the literature.[15]

8-Hydroxybenzo[*c*]chromen-6-one (5c): The procedure was the same as for **5a**. Yield: 0.497 g (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, 1 H), 8.01 (d, 1 H), 7.72 (d, 1 H), 7.46 (t, 1 H), 7.33–7.45 (m, 4 H) ppm.

8-Chlorobenzo[*c*]chromen-6-one (5d): The procedure was the same as for **5a**. Yield: 0.412 g (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, 1 H), 8.08 (d, 1 H), 8.03 (d, 1 H), 7.78 (d, 1 H), 7.52 (t, 1 H), 7.34–7.40 (m, 2 H) ppm. This compound has been reported in the literature.[15]

8-Nitrobenzo[*c*]chromen-6-one (5e): The procedure was the same as for **5a**. Yield: 0.692 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (d, 1 H), 8.64 (dd, 1 H), 8.32 (d, 1 H), 8.13 (dd, 1 H), 7.63 (t, 1 H), 7.42–7.47 (m, 2 H) ppm. This compound has been reported in the literature.[16]

4,6-Difluoro-8-nitrobenzo[*c*]chromen-6-one (5f). Preparation on Multi-Kilogram Scale: Aluminum chloride (16.7 kg, 125.4 mol) was suspended in dichloromethane (48 L). To this suspension, trimethylammonium chloride (6.0 kg, 62.7 mol) was added in portions at 5 °C. To the resulting solution, a solution of methyl 2-(3,5-difluoro-2-methoxyphenyl)-5-nitrobenzoate (**3f**) (6.75 kg, 20.9 mol) in dichloromethane (10 L) was added within 60 minutes. The reaction mixture was stirred at ambient temperature. After 20 hours the reaction was complete according to HPLC analysis and the reaction mixture was poured into water (145 L). The dichloromethane was distilled and the remaining suspension was stirred overnight. The suspension was filtered and the crystals were washed three times with water (15 L). The crystals were dried on a filter. Yield: 5.63 kg of **5f** (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (d, 1 H), 8.68 (dd, 1 H), 8.22 (d, 1 H), 7.61 (dt, 1 H), 7.21 (m, 1 H) ppm.

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