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Recyclable Selective Palladium-Catalyzed Synthesis of Five-, Six- or Seven-Membered Ring Lactones and Lactams by Cyclocarbonylation in Ionic Liquids

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Abstract: The ionic liquids, BMIM PF_6 or BMIM NTf_2, are used successfully for the palladium-catalyzed cyclocarbonylation of 2-allylphenols and anilines, 2-vinylphenols, and 2-aminostyrenes. The reaction proceeds cleanly and efficiently to afford high yields of lactones or lactams with good or excellent selectivity for one isomer. The ionic liquid containing the palladium catalyst, and ligand, is recyclable in all cases.

Keywords: cyclocarbonylation; ionic liquids; lactams; lactones; palladium catalyst

Introduction

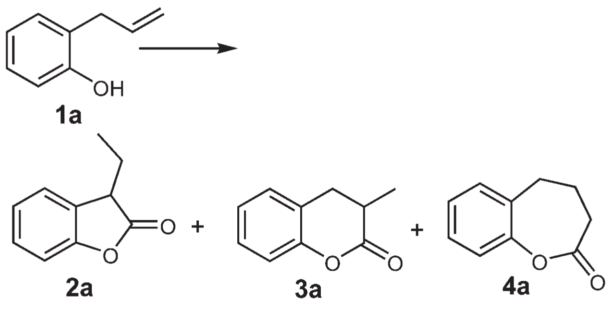
Recently, cyclocarbonylation reactions catalyzed by transition metal complexes have attracted considerable interest as a method to prepare heterocycles,[1] some of which are of pharmacological interest.[2] We have previously reported that the regioselective cyclocarbonylation of 2-allylphenols and anilines, 2-vinylphenols, and 2-aminostyrenes, using palladium catalysts such as $Pd(OAc)_2$ or $Pd(PCy_3)_2(H)(H_2O)^+BF_4^-$, affords five-, six- or seven-membered ring lactones or lactams in excellent yield and selectivity.[3] The selectivity depends on the nature of the catalyst, ligand, relative pressure of gases and the solvent. As catalyst recyclability is a valuable reaction property, we have developed cyclocarbonylation processes using dendrimer-palladium complexes as catalysts, which could be recycled for 3–8 runs.[3f,g,4]

Ionic liquids (IL)[5] have excellent properties including non-volatility, high stability and easy recyclability, and have been widely used as environmentally benign reaction media for catalyst recovery and recycling.[6] We now report that the ionic liquids, 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM PF_6) and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imides (BMIM NTf_2), can be employed for the selective synthesis of five-, six- or seven-membered ring lactones or lactams by palladium-catalyzed cyclocarbonylation. The reaction proceeds cleanly and efficiently to afford high yields of lactones or lactams with good or excellent selectivity for one isomer. The ionic liquid containing the palladium catalyst, and ligand, is recyclable in all cases.

Results and Discussion

Cyclocarbonylation of 2-Allylphenols

Initially, 2-allylphenol **1a** was selected as the model substrate for reaction optimization (Scheme 1). Reaction of 2-allylphenol **1a** with a 1/1 ratio of CO and H_2, 2% mol of $Pd_2(dab)_3{\cdot}CHCl_3$, and 8% mol of 1,4-bis-(diphenylphosphino)butane (dppb) in BMIM PF_6 at 90°C for 20 h afforded lactones in 84% yield, with 77% selectivity for the seven-membered ring lactone **4a** and 23% of the 5- and 6-membered ring isomers (Table 1, entry 3). Although other palladium catalysts such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, and $PdCl_2$



Scheme 1. *Reaction conditions:* $Pd_2(dba)_3{\cdot}CHCl_3$ (2%), dppb (8%), CO (300 psi), H_2 (300 psi), IL, *T*, 20 h.

Table 1. Cyclocarbonylation of 2-allylphenol in various ionic liquids (IL).[a]

Entry	IL (amount)	T [°C]	Conversion [%]	Yield [%][b]	Product Distribution [%][c] **2**	**3**	**4**
1	BMIM PF_6 (1.3 g)	120	100	52	15	33	52
2	BMIM PF_6 (2.5 g)	120	100	83	12	45	43
3	BMIM PF_6 (2.5 g)	90	100	84	8	15	77
4	BMIM BF_4 (2.5 g)	90	100	80	18	60	22
5	BMIM NTf_2 (2.5 g)	90	100	70	3	39	58
6	BMIM Cl (2.5 g)	90	NR[d]				

[a] *Reaction conditions:* 2-allylphenol (0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol), dppb (0.04 mmol), CO (300 psi), H_2 (300 psi), reaction time (20 h).

[b] Isolated yield.

[c] The ratio of **2**/**3**/**4** was determined by ^1H NMR spectroscopy.

[d] No reaction.

$(PhCN)_2$ could be employed for this reaction, $Pd_2(dba)_3 \cdot CHCl_3$ was the most effective cyclocarbonylation catalyst.

Other ionic liquids were also investigated for the cyclocarbonylation reaction (Table 1). While the reaction did not occur in BMIM Cl, the cyclocarbonylation of 2-allylphenol proceeded smoothly in BMIM PF_6, BMIM BF_4 and BMIM NTf_2 to generate lactones in good total yield. However, only BMIM PF_6 at 90 °C gave good product selectivity for the seven-membered lactone (Table 1, entries 3–6). This different product distribution may be due to the sensitivity of the isomerization reaction of 2-allylphenol to solvent polarity,[3a] which could result in the formation of 5- or 6-membered ring lactones. The optimized conditions, involving the use of 2% mol of $Pd_2(dba)_3 \cdot CHCl_3$, and 8% mol of dppb in BMIM PF_6 at 90 °C, were employed to study the recyclability of the system of catalyst, ligand and ionic liquid. After isolation of the product by simple extraction with toluene, the ionic liquid containing the palladium catalyst and ligand was reused for next run. It can be recycled 4 times with only a slight loss of activity (Table 2, entries 4–7).

The cyclocarbonylation reaction in BMIM PF_6 was applied to a variety of 2-allylic phenols, and the results are presented in Table 2. 2-Allylphenols **1b** and **1c**, each containing a methyl group on the allyl chains

Table 2. Cyclocarbonylation of 2-allylphenols in BMIM PF_6.[a]

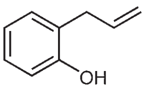
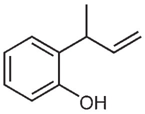
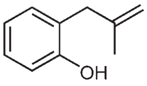
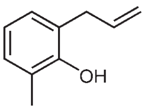
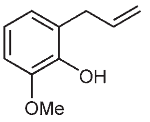
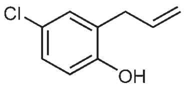
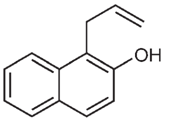
Entry	Substrate		Run	Time [h]	Conversion [%]	Yield [%][b]	Product Distribution [%][c]		
							2	**3**	**4**
1		**1a**	1	20	100	84	8	15	77
2			2	20	100	93	3	37	60
3			3	20	100	72	9	60	31
4			1[d]	20	90	80	1	26	73
5			2[d]	20	100	88	3	37	60
6			3[d]	20	100	84	15	53	32
7			4[d]	45	100	70	18	65	17
8		**1b**	1	24	100	92	0	5	95
9			2	24	100	97	0	5	95
10			3	24	100	85	0	6	94
11			4	45	100	86	0	11	89
12			5	45	100	80	0	23	77
13		**1c**	1[d]	48	89	88	4	0	96
14			2[d]	48	98	97	6	0	94
15			3[d]	52	95	78	9	0	91
16			4[d]	52	100	73	23	0	77
17			1	46	98	95	7	0	93
18		**1d**	1	24	100	91	0	20	80
19			2	24	100	95	0	20	80
20			3	24	100	95	0	20	80
21			4	37	100	90	0	20	80
22			5	45	100	96	0	20	80
23			6	45	100	90	0	22	78

Table 2. (Continued)

Entry	Substrate		Run	Time [h]	Conversion [%]	Yield [%][b]	Product Distribution [%][c]		
							2	**3**	**4**
24		**1e**	1	45	100	91	0	15	85
25			2	45	100	94	0	15	85
26			3	45	100	94	0	15	85
27			4	68	100	89	0	20	80
28			5	68	100	89	0	21	79
29			6	68	100	89	0	21	79
30			7	68	86	78	2	22	76
31		**1f**	1	24	100	93	0	17	83
32			2	24	100	92	0	24	74
33			3	24	100	95	2	36	62
34			4	45	100	94	3	46	51
35		**1g**	1	24	100	92	0	13	87
36			2	24	100	96	0	17	83
37			3	24	100	97	0	19	81
38			4	45	100	90	0	19	81

[a] *Reaction conditions:* substrate (0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol), dppb (0.04 mmol), CO (300 psi), H_2 (300 psi), temperature (90 °C).

[b] Isolated yield.

[c] The ratio of **2**/**3**/**4** was determined by ^1H NMR spectroscopy.

[d] CO (500 psi), H_2 (100 psi).

were converted into seven-membered ring lactones in excellent yield and selectivity with small amounts of six-membered or five-membered ring lactones as by-products. The reaction of 2-allylphenols **1d** and **1e** containing a methyl or methoxy group in the 6-position gave lactones in good selectivity for the seven-membered ring product, while the selectivity was appreciably lower using 2-allyl-4-chlorophenol **1f** as the reactant. Fine selectivity for the seven-membered ring lactone was also obtained for 1-allyl-2-naphthol **1g.** In all cases, the ionic liquid containing the catalyst and ligand could be recycled and reused for 4–7 runs. Interestingly, after recycling, the product distribution changed substantially, especially for allylphenols **1a** and **1f**. It is conceivable that an N-heterocyclic carbene complex of palladium[6a,7] was formed during the reaction, which facilitated the isomerization of some allylphenol to form the 5- or 6-membered ring lactone.[3a]

Cyclocarbonylation of 2-Vinylphenols

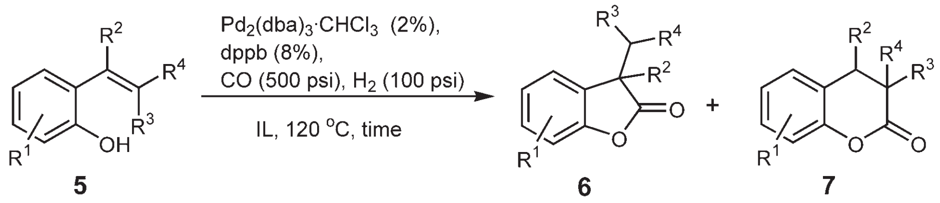
The cyclocarbonylation reaction was next applied to 2-vinylphenols. The reactions in an ionic liquid were investigated at 120 °C and the results are presented in Table 3. Although treatment of 2-vinylphenol **5a** with a 5/1 mixture of CO/H_2, 2% mol of $Pd_2(dba)_3 \cdot CHCl_3$, and 8% mol of dppb in BMIM PF_6 at 120 °C for 45 h produced **6a** and **7a** in a ratio of 1/1 and in 74% yield, the cyclocarbonylation of the 2-isopropenylphenol **5b** under the same conditions resulted in the generation of the six-membered ring lactone as the sole product in 73–80% yield. Other isopropenylphenols also gave **7** in good yields. In contrast, the reaction of 2-propenylphenol **5e** in BMIM PF_6 gave lower reaction selectivity and yield (Table 3, entries 17 and 18). Using BMIM NTf_2 as the ionic liquid gave higher lactone yields, good recyclability for five runs, but with similar 5/6-membered ring selectivity (Table 3, entries 19–23). Ring-substituted 2-propenylphenols, **5f** and **5g**, gave similar results to **5e**. Interestingly, the 1,1-disubstituted phenolic olefin **5h** gave the five-membered lactone in excellent yield and selectivity (Table 3, entries 33–37).

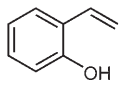
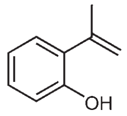
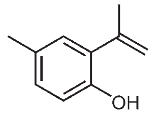
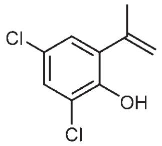
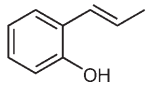
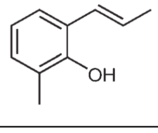
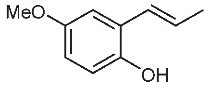
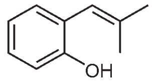
Cyclocarbonylation of 2-Aminostyrenes and 2-Allylanilines

The effectiveness of the system of palladium catalyst/ionic liquid was further demonstrated with the recyclable synthesis of lactams by cyclocarbonylation of 2-aminostyrenes and 2-allylanilines. The six-membered ring lactam is the major product of these carbonylation reactions and the results are presented in Table 4 and Table 5.

While the cyclocarbonylation reaction of 2-aminostyrene **8a** gave lower yields of the lactams **9a** and **10a** using a 5/1 mixture of CO and H_2, in the absence of hydrogen, treatment of 2-aminostyrene **8a** with CO, $Pd_2(dba)_3 \cdot CHCl_3$ and dppb in BMIM PF_6 at 90 °C for

Table 3. Cyclocarbonylation of 2-vinylphenols in BMIM PF_6 or BMIM NTf_2.[a]



Entry	Substrate		IL	Run	Time [h]	Conversion [%]	Yield [%][b]	Product Distribution [%][c]	
								6	**7**
1		**5a**	BMIM PF_6	1[d]	45	35	14	>98	
2				1	45	100	74	50	50
3			BMIM NTf_2	1	45	100	81	45	55
4				2	45	100	85	45	55
5				3	45	100	81	50	50
6				4	64	100	78	50	50
7		**5b**	BMIM PF_6	1	45	84	73	0	100
8				2	45	100	75	0	100
9				3	45	100	80	0	100
10				4	68	100	80	0	100
11		**5c**	BMIM PF_6	1	45	89	77	0	100
12				2	45	100	80	0	100
13				3	45	100	85	0	100
14		**5d**	BMIM PF_6	1	45	87	83	0	100
15				2	45	98	89	0	100
16				3	45	93	70	0	100
17		**5e**	BMIM PF_6	1	45	68	52	61	39
18				2	45	52	41	59	41
19			BMIM NTf_2	1	45	100	88	63	37
20				2	45	100	91	75	25
21				3	45	100	88	64	36
22				4	60	100	86	72	28
23				5	60	100	89	72	28
24		**5f**	BMIM NTf_2	1	45	100	92	72	28
25				2	45	100	89	72	28
26				3	45	100	93	72	28
27				4	60	86	78	72	28
28		**5g**	BMIM NTf_2	1	45	100	89	76	24
29				2	45	100	89	66	34
30				3	45	100	86	66	34
31				4	60	100	90	68	32
32				5	60	100	88	71	29
33		**5h**	BMIM NTf_2	1	60	95	90	87	13 (**4c**)
34				2	60	95	92	87	13 (**4c**)
35				3	60	93	88	85	15 (**4c**)
36				4	70	90	85	85	15 (**4c**)
37				5	70	85	80	88	12 (**4c**)

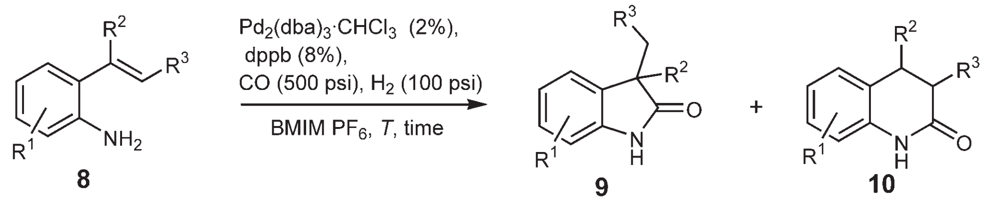
[a] *Reaction conditions:* substrate (0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol), dppb (0.04 mmol), CO (500 psi), H_2 (100 psi), temperature (120 °C).

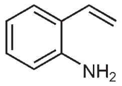
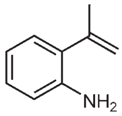
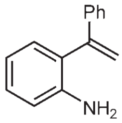
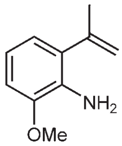
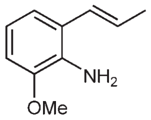
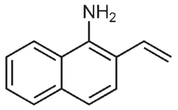
[b] Isolated yield.

[c] The ratio of **6**/**7** was determined by ^1H NMR spectroscopy.

[d] 90 °C.

Table 4. Cyclocarbonylation of 2-aminostyrenes in BMIM PF_6 or BMIM NTf_2.[a]



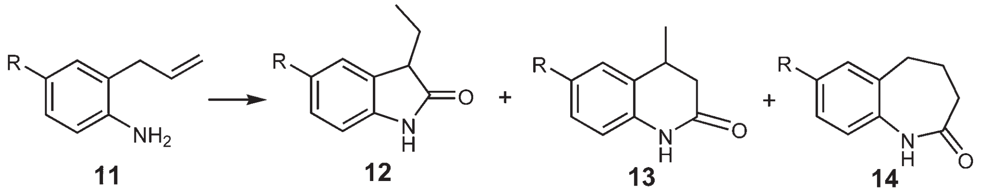
Entry	Substrate		Run	T [°C]	Time [h]	Conversion [%]	Yield [%][b]	Product Distribution [%][c]	
								9	**10**
1		**8a**	1	90	45	100	78	21	79
2			1[d]	90	45	100	87	20	80
3			2[d]	90	45	100	95	20	80
4			3[d]	90	45	100	95	20	80
5			4[d]	90	64	100	90	20	80
6		**8b**	1	90	45	100	91	0	100
7			2	90	45	100	95	0	100
8			3	90	45	100	90	0	100
9			4	90	45	100	86	0	100
10		**8c**	1	120	45	93	87	0	100
11			2	120	45	100	96	0	100
12			3	120	45	100	96	0	100
13			4	120	64	63	60	0	100
14		**8d**	1	90	45	100	86	0	100
15			2	90	45	100	91	0	100
16			3	90	45	100	94	0	100
17			4	90	64	100	91	0	100
18			5	90	68	100	91	0	100
19			6	90	68	100	88	0	100
10		**8e**	1	120	45	100	94	42	58
21			2	120	45	100	95	42	58
22			3	120	45	100	93	42	58
23			1[e]	120	45	100	82	32	68
24			2[e]	120	45	100	87	32	68
25			3[e]	120	45	100	85	32	68
26		**8f**	1	90	45	100	90	15	85
27			2	90	45	100	93	15	85
28			3	90	45	100	93	17	83
29			4	90	64	100	89	20	80
30			5	90	68	100	89	20	80

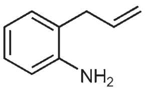
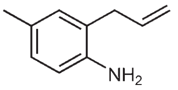
[a] *Reaction conditions:* substrate (0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol), dppb (0.04 mmol), CO (500 psi), H_2 (100 psi).
[b] Isolated yield.
[c] The ratio of **9**/**10** was determined by ^{1}H NMR spectroscopy.
[d] Only CO (600 psi).
[e] In BMIM NTf_2.

45 h resulted in the formation of the six-membered ring lactam **10a** in fine yield and good selectivity (Table 4, entries 2–5). Using a 5/1 mixture of CO and H_2, the reaction of isopropenylanilines **8b–d** afforded the six-membered ring lactams in excellent yield and good recyclability. However, the cyclocarbonylation of 2-propenylaniline **8e** was less selective than those of **8a–d** either in BMIM PF_6 or in BMIM NTf_2. 1-Amino-2-vinylnaphthalene **8f** showed analogous reactivity, selectivity and recyclability to **8a**.

Finally, the reaction of 2-allylanilines, **11a** and **11b**, using a 1/1 mixture of CO and H_2 at 90 °C, gave lactams in excellent yields, but in rather low selectivity for the six-membered ring product (Table 5).

Table 5. Cyclocarbonylation of 2-allylanilines in BMIM PF_6.[a]



Entry	Substrate		Run	Time [h]	Conversion [%]	Yield [%][b]	Product Distribution [%][c]		
							12	**13**	**14**
1		**11a**	1	45	100	86	14	57	29
2			2	45	100	96	18	61	21
3			3	45	100	94	17	64	19
4			4	64	100	93	16	66	18
5		**11b**	1	45	100	90	10	53	37
6			2	45	100	94	16	60	24
7			3	45	100	98	18	58	24
8			4	64	100	96	18	55	27

[a] *Reaction conditions:* substrate (0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.01 mmol), dppb (0.04 mmol), CO (300 psi), H_2 (300 psi), temperature (90 °C).

[b] Isolated yield.

[c] The ratio of **12**/**13**/**14** was determined by ^{1}H NMR spectroscopy.

Conclusions

In conclusion, the ionic liquids, BMIM PF_6 or BMIM NTf_2, are excellent reaction media for the palladium-catalyzed cyclocarbonylation of 2-allylphenols and anilines, 2-vinylphenols, and 2-aminostyrenes. Different ring sizes were favoured, subject to the nature of the reactant, and to steric effects. The ability to recycle these reactants, with little deleterious effects, is noteworthy.

Experimental Section

Representative Procedure for the Cyclocarbonylation Reaction

A mixture of 2-allylphenol **1a** (67 mg, 0.5 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (10 mg, 0.01 mmol), 1,4-bis(diphenylphosphino)butane (17 mg, 0.04 mmol), and BMIM PF_6 (2.5 g) was charged to a 45 mL autoclave. The autoclave was purged, pressurized with CO (300 psi) and H_2 (300 psi), and stirred at 90 °C for 20 h. The reaction mixture was cooled to room temperature, extracted with toluene (8 times), and concentrated by rotary evaporation to afford the mixture of lactones **2a**, **3a**, and **4a** (68 mg, 84 %). The mixture was further purified by preparative TLC using a 1/9 mixture of ethyl acetate and hexane as eluent to afford the following products in the indicated, isolated yields: **4a** (49 mg, 60 %), **3a** (10 mg, 12 %), and **2a** (5 mg, 6 %). After removal of toluene under vacuum, the ionic liquid containing catalyst and ligand was reused for subsequent cycles.

The following lactones and lactams are known compounds and their NMR spectral data were consistent with the literature data: **2a–d**, **2f**, **g**, **3a–d**, **3f**, **g**, **4a–d**, **4f**, **g**, **9a**, **10a**, **9e**, **10e**, **12a**, **b**, **13a**, **b**, **14a**, **b**;[4a] **7b–d**;[4d] **10b–d**;[4e] and **10f**.[8]

Characterization Data for New Compounds

8-Methoxy-3-methylchroman-2-one (3e): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.37$ (d, $J = 6.3$ Hz, 3H), 2.72–2.99 (m, 3H), 3.88 (s, 3H), 6.75 (d, $J = 8.7$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 7.03 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.3$, 31.8, 34.0, 56.0, 110.9, 119.4, 124.0. 124.1, 140.9, 147.4, 170.9; HR-MS (EI): $m/z = 192.0803$, calcd. for $C_{11}H_{12}O_3$: 192.0786.

9-Methoxy-4,5-dihydro-3*H*-benzo[*b*]oxepin-2-one (4e): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.14$–2.21 (m, 2H), 2.48 (t, $J = 7.2$ Hz, 2H), 2.82 (t, $J = 7.2$ Hz, 2H), 3.86 (s, 3H), 6.77 (dd, $J = 7.6$ Hz, 1.6 Hz, 1H), 6.88 (dd, $J = 8.4$ Hz, 1.2 Hz, 1H), 7.10 (t, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.5$, 28.2, 31.1, 56.0, 111.4, 121.0, 126.0, 131.4, 140.6, 149.6, 171.3; HR-MS (EI): $m/z = 192.0779$, calcd. for $C_{11}H_{12}O_3$: 192.0786.

3-Ethyl-5-methoxy-3*H*-benzofuran-2-one (6g): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.4$ Hz, 3H), 1.97–2.13 (m, 2H), 3.69 (t, $J = 6.1$ Hz, 1H), 6.79–6.82 (m, 2H), 7.01–7.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.1$, 24.2, 45.2, 55.8, 110.4, 111.0, 113.3, 128.1, 147.8, 156.5, 177.5; HR-MS (EI): $m/z = 192.0780$, calcd. for $C_{11}H_{12}O_3$: 192.0786.

6-Methoxy-3-methylchroman-2-one (7g): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.36$ (d, $J = 6.4$ Hz, 3H), 2.71–2.83 (m, 2H), 2.87–2.94 (m, 1H), 3.78 (s, 3H), 6.69 (d, $J = 2.8$ Hz, 1H), 6.76 (dd, $J = 9.0$ Hz, 2.8 Hz, 1H), 6.96 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.4$, 31.9. 34.1, 55.6, 113.0, 113.1, 117.3, 123.8, 145.7, 156.0, 171.7; HR-MS (EI): $m/z = 192.0788$, calcd. for $C_{11}H_{12}O_3$: 192.0786.

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