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PHENYLPHOSPHINIC ACID-PROMOTED ADDITION OF ISOCYANIDE TO 1-METHOXYISOCHROMAN DERIVATIVES

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The paper is dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday.

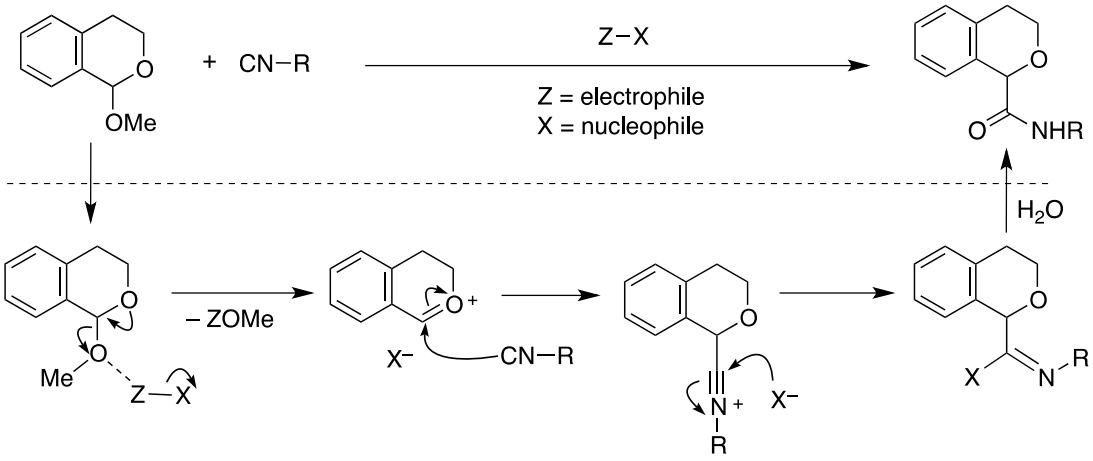
Abstract – A synthetic method for preparation of isochroman-1-carboxylamides in good to high yields by addition of isocyanides to 1-methoxyisochroman derivatives in the presence of phosphinic acid was developed. A wide range of 1-methoxyisochroman derivatives and isocyanides were suitable for this reaction.

INTRODUCTION

Isochromans play an interesting role in heterocyclic chemistry because they occur in a wide variety of natural products and possess varying biological activities. Some isochroman derivatives possess hypotensive,[1] antitumor,[2] and growth-regulating activities;[3] others have a specific effect on the dopaminergic system.[4] Most of these compounds have a substituent at the C1 position of the isochroman moiety. Thus, the development of practical methods for the synthesis of isochromans must consider the presence of substituents at this C1 position. Some reliable methods involving asymmetric synthesis have been reported.[5,6b] Isochroman-1-carboxylic acid and its derivatives are of particular interest as building blocks of modified peptides and other pharmacologically active compounds.[6] This report describes the addition of isocyanides to oxocarbenium ions generated from 1-methoxyisochroman derivatives and promoted by phenylphosphinic acid to give the corresponding isochroman-1-carboxylamide derivatives in good to high yields.

In general, Passerini reactions require a carboxylic acid that activates an aldehyde and traps a nitrilium ion to form an acyloxylated intermediate. Subsequent acyl transfer leads to the corresponding α-acyloxy amide. Therefore, a carboxylic acid is usually a necessary component of the sequence during Passerini

synthesis involving reaction of an isocyanide with an aldehyde. This requirement for the carboxylic acid, however, limits the application of the reaction and precludes the synthesis of a broad range of molecules. overcome this limitation, a compound composed of an electrophile (Z) and a nucleophilic group (X) (referred to as Z–X) was thought to be capable of performing the same function as the carboxylic acid in a Passerini-type reaction (Scheme 1). Based on this hypothesis, an *O*-silylative Passerini reaction involving borinic acid-catalyzed α-addition of isocyanide, an *O*-phosphinative Passerini reaction, and an *O*-sulfinative Passerini reaction have been developed.[7] These reports prompted investigation of the utility of the oxocarbenium ion generated from 1-methoxyisochroman for effective synthesis of the isochroman-1-carboxylamide derivatives (Scheme 1).



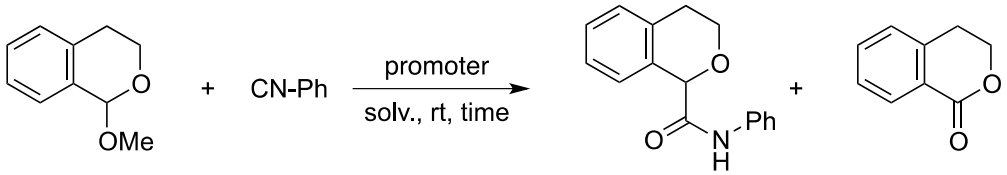
Scheme 1. Hypothetical modified Passerini-type reaction mechanism for generation of an oxocarbenium ion

RESULTS AND DISCUSSION

Initially, the feasibility of using TMSCl[8] as the Z–X species to induce addition of an isocyanide to a 1-methoxyisochroman derivative was investigated using 1-methoxyisochroman (**1a**) and (**2a**) in the presence of TMSCl in MeCN. The results revealed that isochroman-1-carboxylamide **3aa** was obtained in 40% yield, along with isochromanone **4**[9] (Table 1, entry 1). Subsequently, acid or diphenylborinic acid[7d] was used as a Brønsted acid in MeCN. However, none of the reactions these acids was successful; the reactions either did not proceed or gave a very complex mixture of (entries 2 and 3). In contrast, when the reaction was conducted in the presence of phenylphosphinic the isochroman-1-carboxylamide **3aa** was obtained in 97% yield without the formation of any isochromanone **4** (entry 4). 4-Toluenesulfinic acid[7a] was also applicable to this reaction and resulted in formation of **3aa** in 38% yield (entry 5). A 90% yield of the desired product **3aa** was obtained when 2.0

equiv isocyanide **2a** were used (entry 6). The use of toluene, dichloromethane, diethyl ether, and THF as solvents resulted in sluggish reactions that resulted in lower yields of the product (entries 7–10).

Table 1. Reaction conditions and results for the Passerini-type reactions



1a **2a** **3aa** **4**

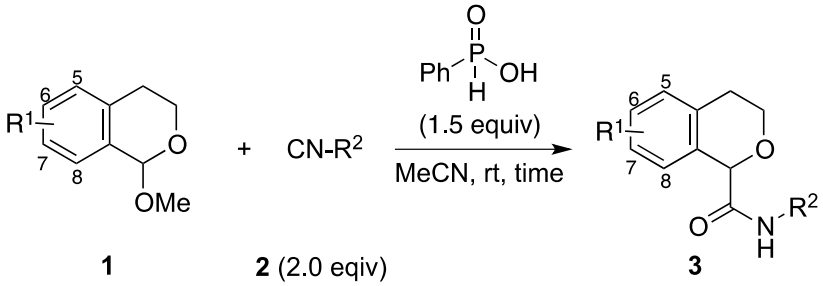
entry[a]	promoter	solvent	**3aa** / yield (%)	**4** / yield (%)
1	TMSCl	MeCN	40	20
2	4-$ClC_6H_4CH_2CO_2H$	MeCN	nr	-
3	Ph_2B-OH	MeCN	trace	-
4	PhP(O)H-OH	MeCN	97	-
5	4-tolS(O)-OH	MeCN	38	-
6[b]	PhP(O)H-OH	MeCN	90	-
7[b]	PhP(O)H-OH	toluene	30	-
8[b]	PhP(O)H-OH	CH_2Cl_2	26	-
9[b]	PhP(O)H-OH	Et_2O	38	-
10[b]	PhP(O)H-OH	THF	33	-

[a] Reaction was conducted using 1.5 equiv promoter and 3.0 equiv **2a**, unless indicated otherwise. [b] 2.0 equiv **2a** used.

To expand the range of isocyanides and 1-methoxyisochroman derivatives that could be used in the Passerini-type reaction, phenylphosphinic acid was used as a promoter; the results are shown in Table 2. In these reactions, optimal amounts of 1-methoxyisochroman derivatives **1a–g** (1.0 equiv) and isocyanides **2a–h** (2.0 equiv) were used in the presence of 1.5 equiv phenylphosphinic acid. The results demonstrated that these conditions allowed the reaction to proceed for a wide variety of 1-methoxyisochroman derivatives and isocyanides, and that most reactions were complete within 24 hours. Reactions of aromatic isocyanides (R^2 = 4-BrC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$) with **1a** gave the products in good to high yields (Table 2, entries 1–4). When the aromatic isocyanides containing an electron-withdrawing group at the *para* position, such as 4-bromophenylisocyanide (**2b**) and 4-nitrophenylisocyanide (**2c**), were used, products were obtained in 74% and 59% yields, respectively (entries 2 and 3). When 4-methoxyphenylisocyanide (**2d**) was used, the desired product **3ad** was obtained in 65% yield (entry 4). Reaction of aliphatic isocyanides **2e**–**2h** (R^2 = *t*-Bu, *t*-Oct, *c*-Hex, and Bn,) with **1a** in the presence of phenylphosphinic acid gave the corresponding products in good yields (entries 5–8). The reactivity of 1-methoxyisochroman derivatives **1** with phenylisocyanide (**2a**) was also examined. For 1-methoxyisochroman, the 5-, 6-, 7-, and 8-methyl substituents all were tolerated, furnishing the

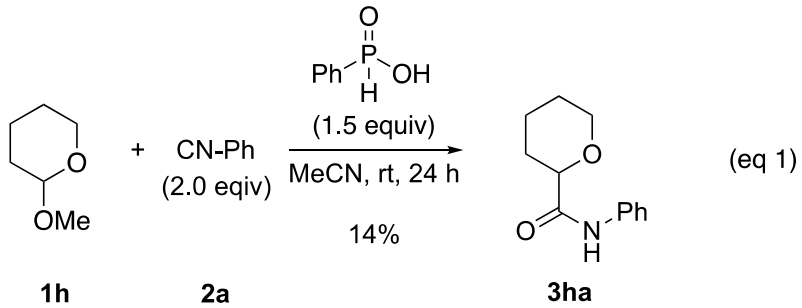
corresponding products in high yields, although the longer reaction time was required in the case of substrate **1e** (Table 2, entries 9–12). Use of the 1-methoxyisochroman **1f** containing an electron-donating group provided product **3fa** in 99% yield (entry 13). However, use of 1-methoxyisochroman **1g** containing an electron-withdrawing group on the aromatic ring exhibited lower reactivity and afforded product **3ga** in 20% yield (entry 14).

Table 2. Range of isocyanides and 1-methoxyisochromans applicable to the Passerini-type reaction



entry[a]	R^1	R^2	time / h	**3** / yield (%)
1	H (**1a**)	Ph (**2a**)	3	90 (**3aa**)
2	H (**1a**)	4-BrC_6H_4 (**2b**)	24	74 (**3ab**)
3	H (**1a**)	4-$O_2NC_6H_4$ (**2c**)	24	59 (**3ac**)
4	H (**1a**)	4-$MeOC_6H_4$ (**2d**)	24	65 (**3ad**)
5	H (**1a**)	*t*-Bu (**2e**)	24	74 (**3ae**)
6	H (**1a**)	*t*-Oct (**2f**)	24	66 (**3af**)
7	H (**1a**)	*c*-Hex (**2g**)	24	69 (**3ag**)
8	H (**1a**)	Bn (**2h**)	24	75 (**3ah**)
9	5-Me (**1b**)	Ph (**2a**)	3	93 (**3ba**)
10	6-Me (**1c**)	Ph (**2a**)	3	89 (**3ca**)
11	7-Me (**1d**)	Ph (**2a**)	3	99 (**3da**)
12	8-Me (**1e**)	Ph (**2a**)	24	79 (**3ea**)
13	6-MeO (**1f**)	Ph (**2a**)	3	99 (**3fa**)
14	7-Br (**1g**)	Ph (**2a**)	3	20 (**3ga**)

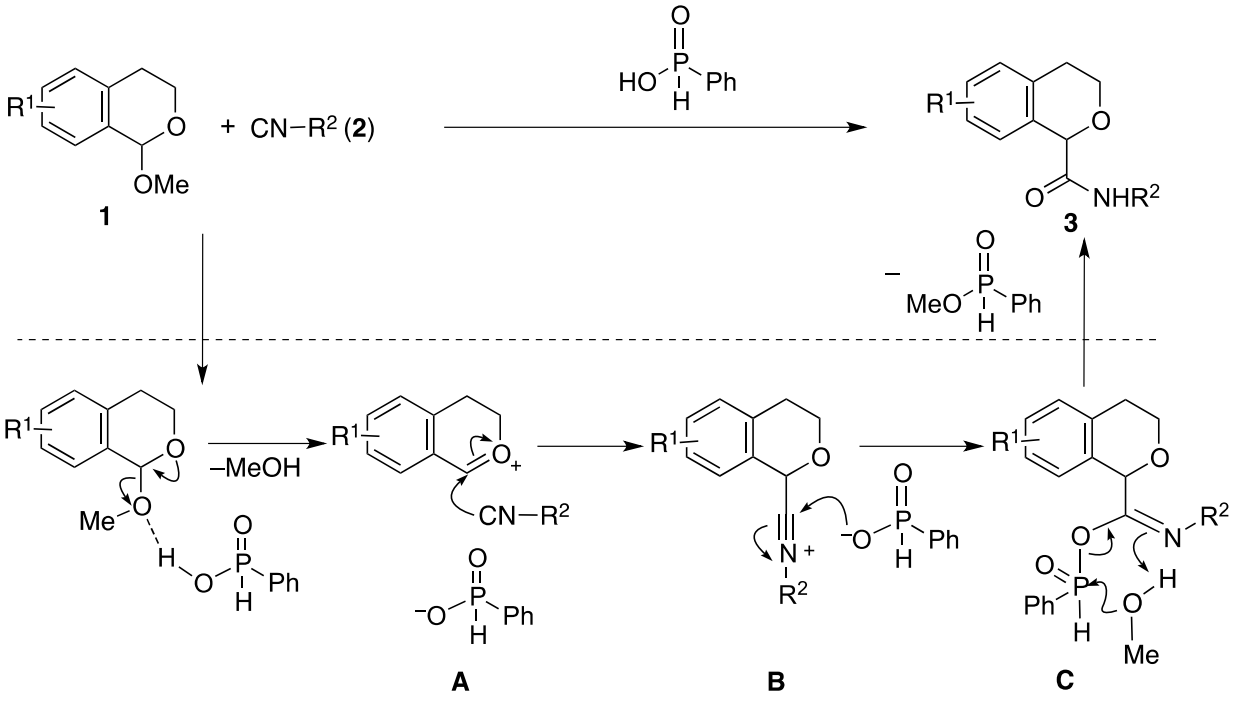
[a] Reaction was conducted using 1.5 equiv of phenylphosphinic acid and 2.0 equiv of **2**.



Reaction conducted using a 2-methoxytetrahydro-2*H*-pyran (**1h**) not fused to the aromatic ring with phenylisocyanide (**2a**) afforded the product **3ha** in 14% yield (eq 1).

The reaction mechanism proposed for the Passerini-type reaction, based on these results, is shown in Scheme 2. 1-Methoxyisochroman is activated by the acidic proton of phosphinic acid (pK_a = 1.75 in H_2O)

followed by the loss of methanol to afford the oxocarbenium ion **A**. Subsequently, nucleophilic attack of the oxocarbenium ion by isocyanide provides nitrilium intermediate **B**, which becomes trapped by the phosphinate anion to afford adduct **C**. Finally, intermediate **C** undergoes solvolysis by methanol to provide product **3**.



Scheme 2. Proposed reaction mechanism

CONCLUSIONS

In conclusion, addition of isocyanides to 1-methoxyisochroman derivatives in the presence of phosphinic acid was achieved to afford the corresponding isochroman-1-carboxylamides in good to high yields. A wide range of 1-methoxyisochroman derivatives and isocyanides were applicable to this reaction.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer. Chemical shifts δ are reported in ppm using TMS as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J) and integration. ^{13}C NMR spectra were recorded on 100 MHz NMR spectrometer. The chemical shifts were determined in the δ-scale relative to $CDCl_3$ (δ = 77.0 ppm). The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. HRMS (DART) was measured with a quadrupole and TOF mass spectrometers. All melting points were measured using a micro melting point apparatus. Dehydrated solvents were purchased for the reactions and used without further desiccation.

General procedure

To a solution of **1** (0.5 mmol) and **2** (1.0 mmol) in MeCN (1 mL), phenylphosphinic acid (0.75 mmol) was added and the whole was stirred at room temperature. After reaction completion (monitored by TLC), satd. $NaHCO_3$ aq was added. Aqueous layer was separated and extracted with $CHCl_3$ (5 mL x 3). Combined organic layers were washed with brine and dried over Na_2SO_4. Concentration and the subsequent purification by silica gel flash column chromatography gave the corresponding isochroman-1-carboxylamides derivatives **3**.

***N*-Phenylisochroman-1-carboxamide (3aa)**

Silica gel column chromatography (hexane/EtOAc = 10/1) gave **3aa** (115 mg, 90% yield) as a white solid of mp 130.2–130.8 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 2.77 (m, 1H), 3.14 (m, 1H), 3.94 (ddd, *J* = 3.2, 11.2, 11.2 Hz, 1H), 4.31 (m, 1H), 5.31 (s, 1H), 7.08–7.16 (m, 2H), 7.22–7.26 (m, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.80 (m, 1H), 8.44 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.3, 63.9, 76.5, 119.6, 121.2, 125.8, 126.3, 127.2, 128.6, 128.7, 131.3, 132.7, 137.2, 168.4. IR (KBr): 3340, 2860, 1670, 1520, 1440, 1110, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{16}NO_2$ $[M+H]^+$: 254.1181. Found: 254.1184.

***N*-(4-Bromophenyl)isochroman-1-carboxamide (3ab)**

Silica gel column chromatography (hexane/EtOAc = 10/1) gave **3ab** (123 mg, 74% yield) as a yellow solid of mp 109.0–110.5 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 2.71 (d, *J* = 16.4 Hz, 1H), 3.07 (m, 1H), 3.86 (ddd, *J* = 3.2, 11.2, 11.2 Hz, 1H), 4.24 (m, 1H), 5.23 (s, 1H), 7.08 (m, 1H), 7.16–7.19 (m, 2H), 7.35 (d, *J* = 9.2 Hz, 2H), 7.41 (d, *J* = 9.2 Hz, 2H), 7.70 (m, 1H), 8.38 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.4, 64.0, 76.5, 116.8, 121.3, 125.9, 126.5, 127.4, 128.8, 131.1, 131.7, 132.7, 136.3, 168.5. IR (KBr): 3320, 2960, 1670, 1590, 1520, 1450, 1290, 1110 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{15}NO_2Br$ $[M+H]^+$: 332.0283. Found: 332.0286.

***N*-(4-Nitrophenyl)isochroman-1-carboxamide (3ac)**

Silica gel column chromatography (hexane/EtOAc = 4/1) gave **3ac** (88 mg, 59% yield) as a yellow solid of mp 147.0–147.4 °C (hexane/EtOAc). ^{1}H-NMR ($CDCl_3$): 2.72 (d, *J* = 16.0 Hz, 1H), 3.09 (m, 1H), 3.88 (ddd, *J* = 3.2, 10.8, 10.8 Hz, 1H), 4.27 (m, 1H), 5.28 (s, 1H), 7.10 (m, 1H), 7.18–7.20 (m, 3H), 7.79 (d, *J* = 9.2 Hz, 2H), 8.14 (d, *J* = 9.2 HZ, 2H), 8.70 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.4, 64.2, 76.5, 119.2, 124.9, 125.7, 126.6, 127.6, 128.9, 130.5, 132.8, 143.1, 143.5, 169.1. IR (KBr): 3340, 3310, 2940, 1700, 1680, 1610, 1530, 1510, 1350, 1290, 1110 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{15}N_2O_4$ $[M+H]^+$: 299.1032. Found: 299.1034.

***N*-(4-Methoxyphenyl)isochroman-1-carboxamide (3ad)**

Silica gel column chromatography (hexane/EtOAc = 4/1) gave **3ad** (92 mg, 65% yield) as a yellow solid of mp 137.4–138.2 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): 2.78 (d, J = 16.4 Hz, 1H), 3.13 (m, 1H), 3.78 (s, 3H), 3.93 (ddd, J = 3.2, 11.2, 11.2 Hz, 1H), 4.31 (m, 1H), 5.30 (s, 1H), 6.85 (d, J = 9.2 Hz, 2H), 7.15 (m, 1H), 7.21–7.24 (m, 2H), 7.46 (d, J = 9.2 Hz, 2H), 7.81 (m, 1H), 8.34 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.4, 55.2, 64.0, 76.5, 113.8, 121.4, 125.9, 126.3, 127.2, 128.6, 130.3, 131.5, 132.7, 156.2, 168.2. IR (KBr): 3340, 3310, 2940, 2870, 1670, 1600, 1530, 1460, 1410, 1250, 1110 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1289. Found: 284.1287.

***N*-(*tert*-Butyl)isochroman-1-carboxamide (3ae)**

Silica gel column chromatography (hexane/EtOAc = 4/1) gave **3ae** (86 mg, 74% yield) as a white solid of mp 55.4–57.3 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 1.33 (s, 9H), 2.73 (d, J = 16.0 Hz, 1H), 3.04 (m, 1H), 3.86 (ddd, J = 3.6, 11.6, 11.6 Hz, 1H), 4.18 (m, 1H), 5.05 (s, 1H), 6.48 (brs, 1H), 7.11 (m, 1H), 7.20 (d, J = 5.6 Hz, 1H), 7.22 (d, J = 5.6 Hz, 1H), 7.72 (m, 1H), ^{13}C NMR ($CDCl_3$): 28.5, 50.7, 63.8, 76.7, 125.9, 126.1, 127.0, 128.5, 132.2, 132.5, 169.5. IR (KBr): 3260, 3070, 2970, 1650, 1550, 1450, 1360, 1260, 1220, 1120 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1498. Found: 234.1494.

***N*-(2,4,4-Trimethylpentan-2-yl)isochroman-1-carboxamide (3af)**

Silica gel column chromatography (hexane/EtOAc = 15/1) gave **3af** (95 mg, 66% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): 0.85 (s, 9H), 1.32 (s, 3H), 1.34 (s, 3H), 1.61 (d, J = 14.8 Hz, 1H), 1.64 (d, J = 14.8 Hz, 1H), 2.65 (d, J = 16.4 Hz, 1H), 2.94 (m, 1H), 3.77 (ddd, J = 3.2, 10.4, 10.4 Hz, 1H), 4.10 (m, 1H), 4.97 (s, 1H), 6.53 (brs, 1H), 7.02 (m, 1H), 7.13 (d, J = 6.0 Hz, 1H), 7.14 (d, J = 6.0 Hz, 1H), 7.67 (m, 1H). ^{13}C NMR ($CDCl_3$): 28.7, 28.8, 29.0, 31.3, 51.9, 54.7, 63.8, 76.7, 126.2, 126.3, 127.0, 128.5, 132.1, 132.7, 169.2. IR (KBr): 3410, 2960, 1680, 1520, 1370, 1260, 1230, 1110 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{18}H_{28}NO_2$ $[M+H]^+$: 290.2120. Found: 290.2126.

***N*-Cyclohexylisochroman-1-carboxamide (3ag)**

Silica gel column chromatography (hexane/EtOAc = 8/1) gave **3ag** (90 mg, 69% yield) as a white solid of mp 118.0–118.8 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 1.06–1.81 (m, 9H), 1.97 (m, 1H), 2.73 (d, J = 16.4 Hz, 1H), 3.05 (m, 1H), 3.75 (m, 1H), 3.87 (ddd, J = 3.6, 10.4, 10.4 Hz, 1H), 4.19 (m, 1H), 5.15 (s, 1H), 6.53 (d, J = 6.8 Hz, 1H), 7.10 (m, 1H), 7.20 (d, J = 5.6 Hz, 1H), 7.21 (d, J = 5.6 Hz, 1H), 7.76 (m, 1H). ^{13}C NMR ($CDCl_3$): 24.7, 25.3, 28.4, 32.9, 47.7, 63.8, 76.3, 125.9, 126.2, 126.9, 128.5, 132.0, 132.6, 169.4. IR (KBr): 3290, 2930, 1650, 1530, 1450, 1380, 1290, 1120 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1651. Found: 260.1656.

_N_-Benzylisochroman-1-carboxamide (3ah)

Silica gel column chromatography (hexane/EtOAc = 8/1) gave **3ah** (100 mg, 75% yield) as a white solid of mp 102.9–104.9 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 2.72 (d, J = 16.4 Hz, 1H), 3.03 (m, 1H), 3.86 (ddd, J = 3.2, 11.2, 11.2 Hz, 1H), 4.19 (m, 1H), 4.37 (dd, J = 6.4, 14.8 Hz, 1H), 4.55 (dd, J = 6.4, 14.8 Hz, 1H), 5.26 (s, 1H), 6.98 (brs, 1H), 7.11 (m, 1H), 7.20–7.33 (m, 7H), 7.79 (m, 1H). ^{13}C NMR ($CDCl_3$): 28.3, 42.8, 63.8, 76.3, 125.9, 126.3, 127.1, 127.2, 127.5, 128.4, 128.5, 131.8, 132.6, 137.9, 170.4. IR (KBr): 3300, 2980, 1660, 1540, 1490, 1450, 1360, 1290, 1250, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338. Found: 268.1343.

5-Methyl-*N*-phenylisochroman-1-carboxamide (3ba)

Silica gel column chromatography (hexane/EtOAc = 10/1) gave **3ba** (121 mg, 93% yield) as a yellow solid of mp 121.4–123.0 °C ((hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 2.19 (s, 3H), 2.62 (m, 1H), 2.85 (m, 1H), 3.80 (ddd, J = 4.0, 11.6, 11.6 Hz, 1H), 4.28 (m, 1H), 5.24 (s, 1H), 7.00–7.10 (m, 3H), 7.23 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.57 (d, J = 7.6 Hz, 1H), 8.32 (brs, 1H). ^{13}C NMR ($CDCl_3$): 18.7, 25.7, 63.7, 76.5, 119.5, 123.2, 124.0, 125.7, 128.5, 128.6, 130.9, 131.0, 135.9, 137.1, 168.3. IR (KBr): 3340, 2860, 1670, 1520, 1440, 1110 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338. Found: 268.1341.

6-Methyl-*N*-phenylisochroman-1-carboxamide (3ca)

Silica gel column chromatography (hexane/EtOAc = 10/1) gave **3ba** (119 mg, 89% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): 2.24 (s, 3H), 2.65 (m 1H), 3.02 (m, 1H), 3.85 (ddd, J = 3.2, 11.2, 11.2 Hz, 1H), 4.22 (m, 1H), 5.20 (s, 1H), 6.89 (s, 1H), 6.97–7.04 (m, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.6 Hz, 1H), 8.35 (brs, 1H). ^{13}C NMR ($CDCl_3$): 20.9, 28.5, 64.1, 76.6, 119.7, 124.2, 125.9, 127.3, 128.4, 128.8, 129.2, 132.6, 137.0, 137.3, 168.7. IR (KBr): 3390, 2920, 2860, 1690, 1600, 1530, 1440, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338. Found: 268.1335.

7-Methyl-*N*-phenylisochroman-1-carboxamide (3da)

Silica gel column chromatography (hexane/EtOAc = 10/1) gave **3da** (132 mg, 99% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$): 2.33 (s, 3H), 2.73 (d, J = 16.4 Hz, 1H), 3.09 (m, 1H), 3.90 (ddd, J = 3.2, 10.8, 10.8 Hz, 1H), 4.30 (m, 1H), 5.27 (s, 1H), 7.01–7.12 (m, 3H), 7.31 (t, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.61 (s, 1H), 8.43 (s, 1H). ^{13}C NMR ($CDCl_3$): 21.2, 28.2, 64.2, 76.7, 119.8, 124.3, 126.3, 128.2, 128.6, 128.9, 129.6, 131.1, 136.1, 137.3, 168.6. IR (KBr): 3390, 2920, 2860, 1680, 1600, 1530, 1440, 1370, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338. Found: 268.1335.

8-Methyl-*N*-phenylisochroman-1-carboxamide (3ea)

Silica gel column chromatography (hexane/EtOAc = 10/1) gave **3ea** (105 mg, 79% yield) as a white solid of mp 156.8–158.8 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 2.29 (s, 3H), 2.75 (ddd, J = 4.8, 9.6, 9.6 Hz, 1H), 2.93 (m, 1H), 3.92 (m, 1H), 4.03 (m, 1H), 5.40 (s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 7.03–7.06 (m, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.25 (t, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 8.28 (brs,1H). ^{13}C NMR ($CDCl_3$): 19.3, 28.6, 63.0, 74.8, 119.5, 124.3, 126.0, 127.6, 128.6, 128.9, 130.1, 133.2, 136.7, 137.5, 168.6. IR (KBr): 3290, 2890, 1660, 1600, 1530, 1440, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$: 268.1338. Found: 268.1338.

6-Methoxy-*N*-phenylisochroman-1-carboxamide (3fa)

Silica gel column chromatography (hexane/EtOAc = 4/1) gave **3fa** (140 mg, 99% yield) as a yellow solid of mp 104.5–105.8 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 2.77 (m, 1H), 3.12 (m, 1H), 3.78 (s, 3H), 3.93 (ddd, J = 3.2, 11.2, 22.0 Hz, 1H), 4.30 (m, 1H), 5.30 (s, 1H), 6.85 (d, J = 9.2 Hz, 2H), 7.13 (m, 1H), 7.12–7.24 (m, 2H), 7.46 (d, J = 9.2 Hz, 2H), 7.81 (m, 1H), 8.34 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.7, 55.0, 63.9, 76.3, 112.4, 113.4, 119.7, 123.5, 124.2, 127.2, 128.8, 134.1, 137.2, 158.6, 168.7. IR (KBr): 3380, 2930, 2860, 1690, 1600, 1520, 1440, 1300, 1240, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{17}H_{18}NO_3$ $[M+H]^+$: 284.1287. Found: 284.1288.

7-Bromo-*N*-phenylisochroman-1-carboxamide (3ga)

Silica gel column chromatography (hexane/EtOAc = 4/1) gave **3ga** (34 mg, 20% yield) as a brown oil. ^{1}H NMR ($CDCl_3$): 2.66 (d, J = 16.8 Hz, 1H), 2.99 (m, 1H), 3.84 (ddd, J = 3.6, 11.2, 11.2 Hz, 1H), 4.23 (m, 1H), 5.17 (s, 1H), 6.94 (d, J = 8.4 Hz, 1H), 7.05 (t, J = 8.4 Hz, 1H), 7.19–7.30 (m, 3H), 7.50 (d, J = 8.4 Hz, 2H), 7.93 (s, 1H), 8.36 (brs, 1H). ^{13}C NMR ($CDCl_3$): 28.0, 63.9, 75.9, 119.8, 120.2, 124.5, 128.9, 129.0, 130.3, 130.5, 131.7, 133.4, 137.1, 167.8. IR (KBr): 3380, 2870, 1690, 1600, 1530, 1440, 1310, 1240, 1180, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{16}H_{15}NO_2Br$ $[M+H]^+$: 332.0289. Found: 332.0286.

***N*-Phenyltetrahydro-2*H*-pyran-2-carboxamide (3ha)**

Silica gel column chromatography (hexane/EtOAc = 4/1) gave **3ha** (14 mg, 14% yield) as a yellow solid of mp 121.0–122.8 °C (hexane/EtOAc). ^{1}H NMR ($CDCl_3$): 1.38–1.59 (m, 4H), 1.89 (m, 1H), 2.12 (m, 1H), 3.49 (m, 1H), 3.83 (dd, J = 2.8, 11.2 Hz, 1H), 4.08 (m, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.6 Hz, 2H), 7.52 (d, J = 7.6 Hz, 2H), 8.26 (brs, 1H). ^{13}C NMR ($CDCl_3$): 23.1, 25.6, 29.1, 68.4, 77.3, 119.6, 124.2, 128.9, 137.4, 169.9. IR (KBr): 3310, 2960, 2850, 1670, 1600, 1530, 1440, 1320, 1260, 1100 cm^{-1}. HRMS–DART (*m/z*): Calcd for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181. Found: 206.1185.

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