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Four-component synthesis of alkyl [2-[(cyclohexylamino)carbonyl]-4-oxo-2*H*-chromen-3(4*H*)-ylidene]methyl 3,4,5,6-tetrahalophthalates *via* a domino *O*-acylation/α-addition cyclization/alcoholysis sequence

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ABSTRACT

A novel protocol was developed for the synthesis of alkyl [2-[(cyclohexylamino)carbonyl]-4-oxo-2*H*-chromen-3(4*H*)-ylidene]methyl 3,4,5,6-tetrahalophthalate derivatives *via* the one-pot, four-component domino *O*-acylation/α-addition cyclization/alcoholysis reaction of tetrahalophthalic anhydrides, 3-formylchromones, cyclohexyl isocyanide and various alcohols. The highlights of this novel cascade reaction include mild reaction conditions, easy workup, and high bond efficiency resulting in the formation of four new bonds (two C—O, one C=O and one C—C) in a single operation.

Multicomponent reactions (MCRs), in which three or more components react in a single synthetic operation to produce complicated molecules with high atom economy, constitute a versatile class of reactions which are widely employed for the synthesis of complex heterocycles and natural products.[1a] Isocyanide-based multicomponent reactions such as the Passenini, Ugi, Groebke-Bienaymé-Blackburn, Orru, and Van Leusen reactions are among the most popular multicomponent condensations due to their diversity of bond-forming processes, functional group tolerance, and high levels of chemo-, regio-, and stereoselectivity.[1b]

The chromone structural scaffold is a common heterocyclic framework present in numerous natural compounds and pharmaceutical molecules.[2] Among these compounds, 2-phenylchromones represent a class of flavonoids which are well known for their varied biological activities, including immunopromoter,[3] anticancer,[4] anti-inflammatory,[5] and anti-diabetic properties.[6] The presence of an acidic functional group at C-2 or C-3 is known to inhibit passive cutaneous anaphylaxis, an allergic reaction which causes asthma, rhinitis and urticaria.[7] For example, cromolyn sodium is a preventive medication for asthma sold under the trade name Intal® (Fig. 1).[8] Replacement of the carboxyl group by a amido moiety has been demonstrated in some cases to result in increased pharmacological activity.[9] Furthermore, 3-methylenechromones and their derivatives have been examined *in vitro* for their ability to inhibit the growth of representative bacteria and fungi.[10]

Although 3-formylchromones can be regarded as α,β-unsaturated aldehydes and ketones, the conjugate addition of carbon nucleophiles to the *C*2-position of the chromone moiety without ring opening or ring transformation has had only limited success.[11] These reactions are typically promoted by Lewis acids such as boron trifluoride[12] and *tert*-butyldimethylsilyl triflate.[13] Our previous synthetic work revealed that the reaction of 3-formychromone and isocyanides proceeded smoothly in the presence of electrophiles such as 3-formylchromone[14a] and isatin derivatives[14b] to give the corresponding (1*Z*)-3-(alkylimino)-1-[(chromone-3-yl)methylene]-1,3-dihydro-9*H*-furo[3,4-*b*]chromen-9-ones and 3-(alkyliminofurochromonyl)-3-hydroxyoxindole, respectively, *via* a cascade [4 + 1]-cycloaddition followed by an activated electrophilic heteroaromatic substitution reaction (Scheme 1).

In this context, we have explored the use of tetrahalophthalic anhydride as an electrophile. Our initial aim was the synthesis of acylated fused aminofurochromones and began with the model reaction of a 3-formyl-6-methylchromone and tetrachlorophthalic anhydride with cyclohexyl isocyanide in MeOH:CH_2Cl_2 (1:5). To our surprise, the products were [2-[(cyclohexylamino)carbonyl]-6-methyl-4-oxo-2*H*-chromen-3(4*H*)-ylidene]methyl methyl 3,4,5,6-tetrachlorophthalate **5a** with a chiral carbon at C-2 and a methylenechromone subunit.

Encouraged by this unexpected observation, additional reactions of 3-formylchromones, tetrahalophthalic anhydrides,

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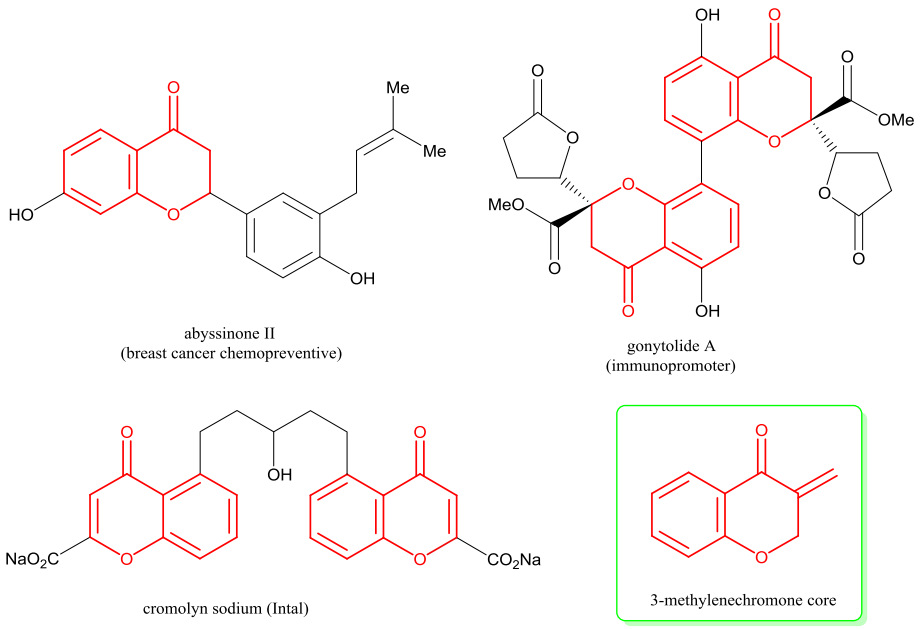
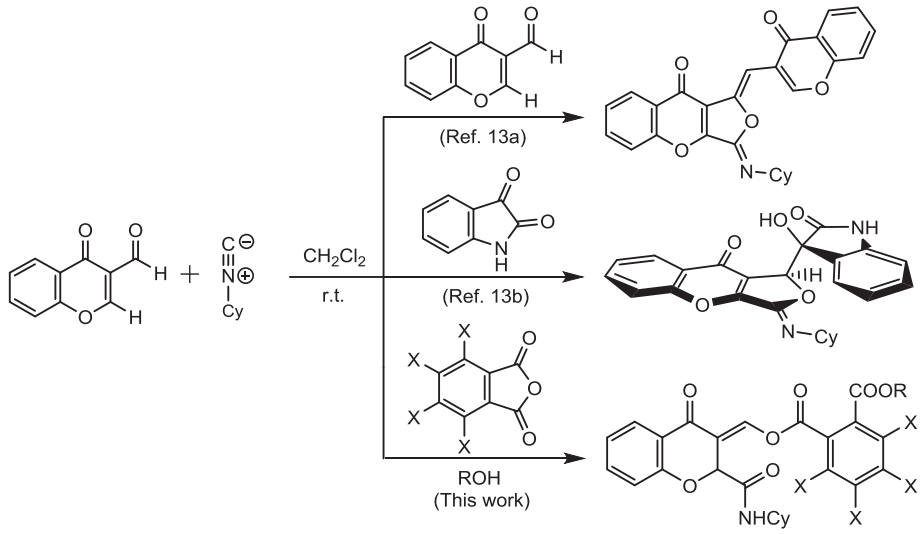


Fig. 1. Representative bioactive chromone derivatives.

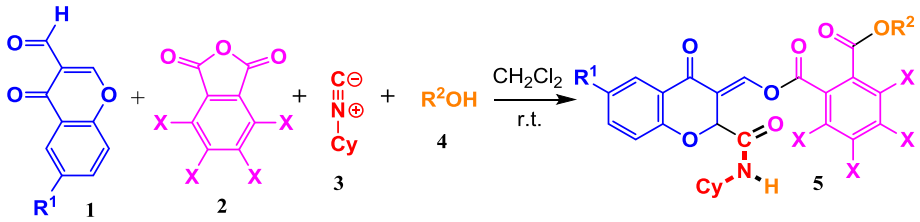


Scheme 1. Recently reported MCRs of cyclohexyl isocyanides and 3-formylchromone in the presence of reactive carbonyl compounds.

cyclohexyl isocyanide and alcohols in CH_2Cl_2 were examined (Table 1). All reactions proceeded to completion within four days, affording products **5a–q** as stable white solids whose structures were supported by elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectroscopy.[15] For example, the IR spectrum of **5a** showed absorptions at 3319 and 3085 cm^{-1} for N—H and vinylic C—H bonds as well as at 1762, 1738, 1665, 1644 and 1619 cm^{-1} indicating the presence of four carbonyls and one olefin functional groups. The ^{1}H NMR spectrum of **5a** consisted of multiplet signals for the cyclohexyl rings (δ_H 1.18–2.05 ppm) and the NH-C*H* resonance (δ_H 3.79–3.82 ppm) as well as four singlets arising from a methyl proton (δ_H 2.46 ppm), methoxy group (δ_H 3.84 ppm), allylic methine (δ_H 6.19 ppm) and vinylic methine (δ_H 8.20 ppm). A fairly broad doublet (δ_H 6.78 ppm, $^3J_{HH}$ = 8.1 Hz) was observed for the cyclohexyl-N*H* group. The chromenyl moiety gave rise to a doublet (δ_H 7.39 ppm, d, $^3J_{HH}$ = 8.5 Hz), a doublet of doublets (δ_H 7.51 ppm, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.1 Hz), and a broad singlet (δ_H 7.99 ppm, br. s) in the aromatic region of the spectrum. The ^{1}H decoupled ^{13}C NMR spectrum of **5a** showed 26 resonances which was in agreement with the proposed structure.

The three 3-formylchromone derivatives (3-formylchromone, 3-formyl-6-methyl-chromone and 6-chlor-3-formylchromone) afforded products **5a–q** in moderate to good yields. Under similar reaction conditions, starting with tetrachlorophthalic anhydride or tetrabromophthalic anhydride, cyclohexyl isocyanide, methanol and 6,8-dichloro-3-formylchromone, in the presence of water the corresponding known product[14a] (1*Z*)-5,7-dichloro-3-(cyclohexylimino)-1-[(6,8-dichloro-4-oxo-4*H*-chromen-3-yl) methylene]-1,3-dihydro-9*H*-furo[3,4-*b*]chromen-9-one was isolated without participation of the tetrahalophthalic anhydride and methanol. A variety of structurally diverse primary and secondary alcohols underwent the one-pot, four-component reaction to afford the corresponding 2-[(cyclohexylamino)carbonyl]-6-methyl-4-oxo-2*H*-chromen-3(4*H*)-ylidene]methyl alkyl 3,4,5,6-tetrachlorophthalate derivatives in good yields. Additionally, both tetrachlorophthalic anhydride and

Table 1
Synthesis of compounds **5a–l**.[a]



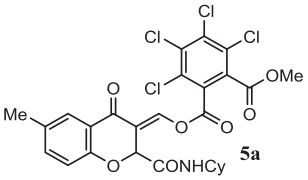
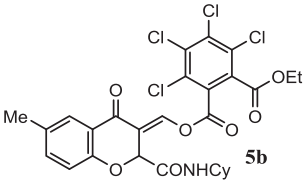
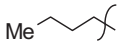
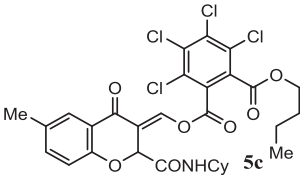
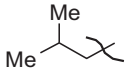
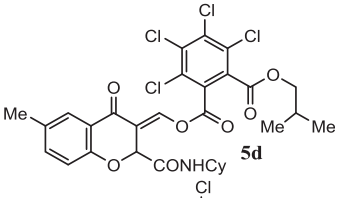
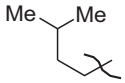
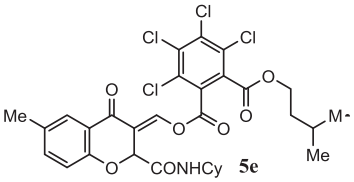
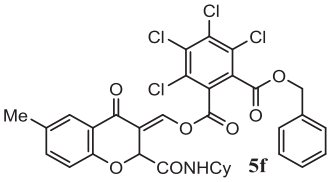
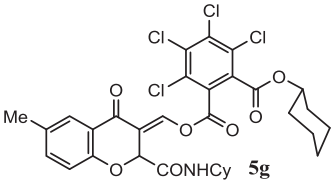
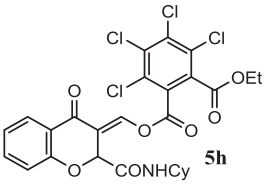
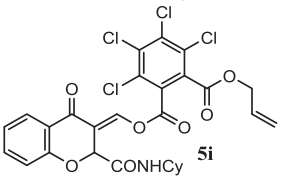
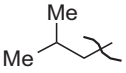
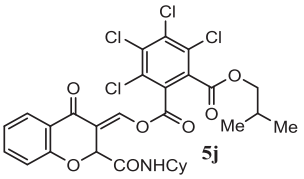
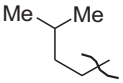
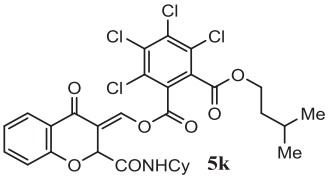
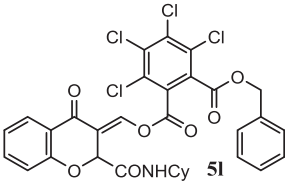
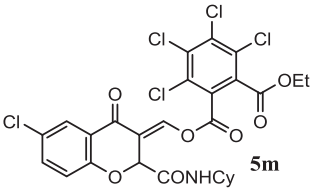
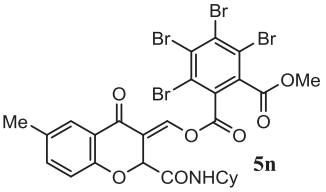
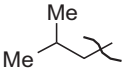
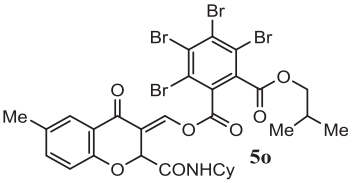
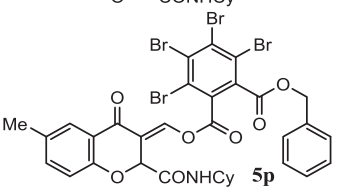
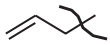
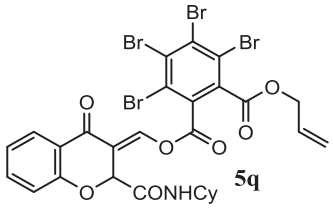
Entry	R^1	X	R^2	Product	Yield **5** (%)[b]
1	Me	Cl	Me	 **5a**	**73**
2	Me	Cl	Et	 **5b**	**81**
3	Me	Cl		 **5c**	**74**
4	Me	Cl		 **5d**	**70**
5	Me	Cl		 **5e**	**75**
6	Me	Cl		 **5f**	**76**
7	Me	Cl		 **5g**	**68**

Table 1 (*continued*)

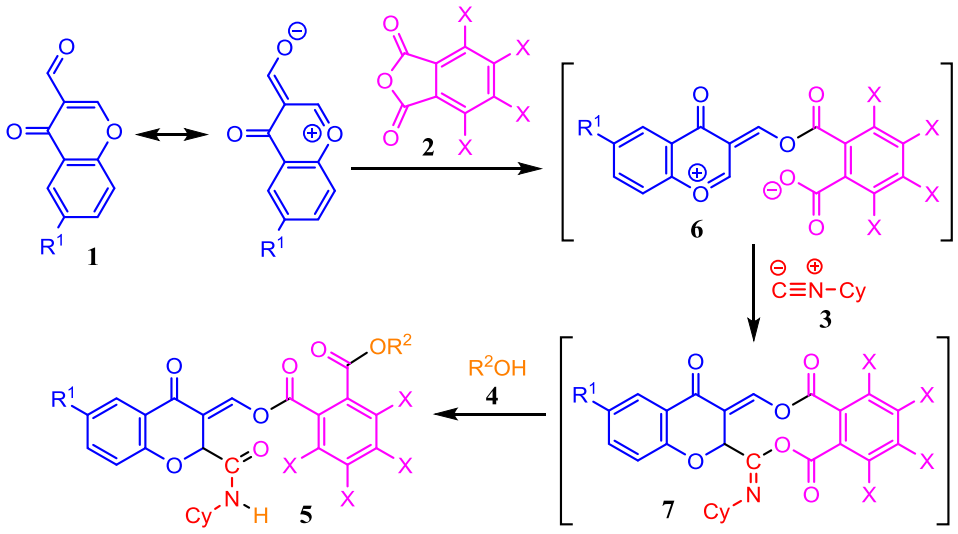
Entry	R^1	X	R^2	Product	Yield **5** (%)[b]
8	H	Cl	Et	 **5h**	**86**
9	H	Cl		 **5i**	**76**
10	H	Cl		 **5j**	**73**
11	H	Cl		 **5k**	**85**
12	H	Cl		 **5l**	**83**
13	Cl	Cl	Et	 **5m**	**80**
14	Me	Br	Me	 **5n**	**72**
15	Me	Br		 **5o**	**73**
16	Me	Br		 **5p**	**79**

(*continued on next page*)

Table 1 (*continued*)

Entry	R^1	X	R^2	Product	Yield **5** (%)[b]
17	H	Br		 **5q**	**71**

[a] Reagents and conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (1.0 mmol), **4** (MeOH or EtOH, 1 mL), CH_2Cl_2 (5 mL), room temperature.
[b] Isolated yield.



Scheme 2. Proposed mechanism for the synthesis of 2-cyclohexylamido-3-methylenechromones **5**.

tetrabromophthalic anhydride tolerated the reaction conditions with good yields. Our attempts to carry out this reaction under the same reaction conditions by using phthalic anhydride and its electron-releasing derivatives such as the 3,6-dimethylanhydride were not successful and the reaction led to intractable mixture. This perhaps implied the lower electrophilicity of these compounds compared to tetrahalophthalic anhydrides.

A possible mechanism for the formation of products **5a–q** is shown in Scheme 2. On the basis of the chemistry of 3-formylchromones,[16] it is reasonable to assume the oxygen atom at the 1-position diminishes electron density on the adjacent C-2 atom *via* an electron push-pull effect and the aldehyde carbonyl group withdraws electrons through the double bond. Hence the oxygen atom of the aldehyde group can be reactive as a nucleophile toward the C2-position of 3-formylchromone as a highly reactive electrophilic site. It is conceivable that the resonance-stabilized oxonium-carboxylate zwitterion **6**, formed by nucleophilic attack of the aldehyde oxygen of 3-formylchromone **1** to the carbonyl group of tetrahalophthalic anhydride **2**, is trapped by cyclohexyl isocyanide **3** to give intermediate **7** *via* an α-addition cyclization reaction. Finally, nucleophilic attack of an alcohol on the imidoyl carboxylate moiety of intermediate **7** gives the 2-cyclohexylamido-3-methylenechromones **5**.

In conclusion, a four-component one-pot reaction was developed for the synthesis of functionalized 2-amido-3-methylenechromones. This protocol allows for the introduction of several functional groups, such as amide, enol ether, and alkyl phthalate groups, as well as double bonds.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.02.037.

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15. *Typical procedure for the synthesis of [2-[(cyclohexylamino)carbonyl]-6-methyl-4-oxo-2H-chromen-3(4H)-ylidene]methyl methyl 3,4,5,6-tetrachlorophthalate* **5a**: To a stirred mixture of tetrachlorophthalic anhydride (0.286 g, 1.0 mmol) and 6-methyl-3-formylchromone (0.188 g, 1.0 mmol) in CH_2Cl_2 (5 mL) and MeOH (1 mL) was added cyclohexyl isocyanide (0.110 g, 1 mmol) *via* syringe at room temperature (25 °C) and the resulting mixture stirred for 4 days. Reaction completion was confirmed by TLC (EtOAc/hexane 1:2). The solvent was removed under reduced pressure and the residue washed with diethyl ether and crystallized from hexane-CH_2Cl_2 (5:1) to give **5a** as a white powder (0.450 g, 73%). m.p. 169–171 °C. IR (KBr) (ν_{max}, cm^{-1}): 3319 (N—H), 3085 (=C—H), 1762, 1738, 1665 and 1644 (C=O), 1619 (C=C). ^{1}H NMR ($CDCl_3$, 300.1 MHz): δ_H 1.18-2.05 (10 H, m, 5 CH_2 of cyclohexyl), 2.46 (3 H, s, CH_3), 3.82 (3 H, s, OCH_3), 3.79-3.84 (1 H, m, NCH), 6.19 (1 H, s, O—CH—C=O), 6.78 (1 H, d, $^3J_{HH}$ 8.1 Hz, N*H*—CH), 7.39 (1 H, d, $^3J_{HH}$ 8.5 Hz, CH_3—C—CH=C*H*), 7.51 (1 H, dd, $^3J_{HH}$ 8.5 Hz, $^4J_{HH}$ 2.1 Hz, CH_3—C—C*H*=CH), 7.99 (1 H, br. s, CH_3—C=C*H*), 8.19 (1 H, s, C=C*H*—O). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ_C 175.9, 165.1, 164.1, 162.5, 156.1, 154.5, 136.5, 136.2, 135.8, 135.5, 132.0, 131.1, 130.8, 130.7, 125.2, 123.6, 118.8, 118.0, 71.2, 53.6, 48.7, 32.8, 32.6, 25.5, 24.8, 20.9. Anal. Calcd. for $C_{27}H_{23}Cl_4NO_7$ (615.28) C 52.71, H 3.77, N 2.28%; Found C 52.95, H 3.71, N 2.33%.
16. Ghosh CK, Patra A. *J Heterocyclic Chem*. 2008;45:1529.