Acyl cyanides as carbonyl heterodienophiles: application to the synthesis of naphthols, isoquinolones, and isocoumarins

Richard Connors, Elisabeth Tran, and Tony Durst

Abstract: Irradiation of 2-methylbenzoyl cyanide (**3***a*) in acetonitrile solution results in the formation of its dimer, which upon loss of HCN gives rise to the cycloadduct **7***a*. The dimerization also proceeds efficiently with derivatives of **3***a* giving adducts **7***b* and **7***c*. When 2-methylaroyl cyanides are photolyzed in the presence of a more reactive acyl cyanide the mixed adducts **8***a–e* are obtained in excellent yields. The cycloadducts **7***a–c* and **8***a–e* react with carbon and nitrogen nucleophiles by a tandem addition–cyclization sequence furnishing substituted naphthols (**10***a* and **10***b*) and isoquinolones (**11***a–d*), respectively. Isocoumarins **12***a* and **12***b* were prepared from the adducts **8***a* and **8***e* by treatment with potassium *tert*-butoxide in THF.

Key words: naphthols, isoquinolones, isocoumarins, synthesis of; acyl cyanides; hetero Diels–Alder.

Résumé : L'irradiation du cyanure de 2-méthylbenzoyle (**3***a*) en solution dans l'acétonitrile conduit à la formation de son dimère qui, par perte de HCN, fournit le cycloadduit **7***a*. La dimérisation se produit aussi d'une façon efficace avec les dérivés du composé **3***a*; elle conduit alors aux composés **7***b* et **7***c*. Lorsqu'on effectue la photolyse des cyanures de 2-méthylaroyle en présence d'un cyanure d'acyle plus réactif, on obtient alors les produits mixtes **8***a–e* avec d'excellents rendements. Les cycloadduits **7***a–c* et **8***a–e* réagissent avec les nucléophiles carbonés et azotés par une séquence de réactions d'addition–cyclisation en tandem qui fournissent respectivement des naphtols (**10***a* et **10***b*) et des isoquinoléines (**11***a–d*) substitués. Par réaction des adduits **8***a* et **8***e* avec du *tert*-butylate de potassium dans le THF, on a préparé les isocoumarines **12***a* et **12***b*.

Mots clés : naphtols, isoquinoléines, isocoumarines, synthèse; cyanures d'acyle; hétéro Diels–Alder.

[Traduit par la rédaction]

Introduction

o-Quinodimethanes (OQDM) have seen extensive application in the synthesis of natural products (1). Diels–Alder reactions of these intermediates have been studied with both alkene- and heterodienophiles. Oppolzer (2) and Kametani et al. (3) have demonstrated that imines, nitriles, and aldehydes can serve as both inter- and intramolecular dienophiles with *o*-quinodimethanes generated via ring openings of benzocyclobutenes. Sammes and co-workers (4) reported that the dienol generated photochemically from 2-methylbenzaldehyde reacted efficiently with ground state aldehydes in a cycloaddition reaction. Other carbonyl-containing functional groups have not been observed as dienophiles in Diels–Alder reactions with *o*-quinodimethanes. Highly reactive ketones, such as ketomalonates, have received limited attention as dienophiles (5); there is only one report of the carbonyl group of an ester participating in a Diels–Alder reaction (6).

Our report (7) of the cycloaddition of both thermally and photochemically generated *o*-quinodimethanes with benzoyl and acetyl cyanide (see Scheme 2), represents the first example in which an acyl cyanide acts in such a capacity. The recent publication by Kessar et al. which describes the synthesis of various 3-aryl-3,4-dihydroisocoumarins and protoberberines involving fluorodesilylation of 2-((trimethylsilyl)-methyl) benzoyl chlorides, **1**, in the presence of aromatic aldehydes and 3,4-dihydroisoquinolium salts (8), is closely related to our work. This group also describes a "dimerization" of the chloride **1** to the isocoumarin **2** when the fluoride treatment was carried out in the absence of other trapping agents (Scheme 1).

In this paper we present a more detailed account of our earlier report including additional reactions involving several new dienes and dienophiles. In addition, considerable synthetic utility of the cycloadducts has also been demonstrated by their use as intermediates in the synthesis of highly functionalized naphthols, isoquinolones, and isocoumarins.

Discussion and results

At the outset of this study, we postulated that photoenolization of 2-methylbenzoyl cyanide (**3***a*) and, especially, some of the more crowded analogs such as 2-methoxy-6-methylbenzoyl cyanide **3***b* might lead to a benzocyclobutenone such as **6**, by electrocyclization of the intermediate dienol **4** to **5** followed by HCN loss (Scheme 3). Sammes and co-workers demon-

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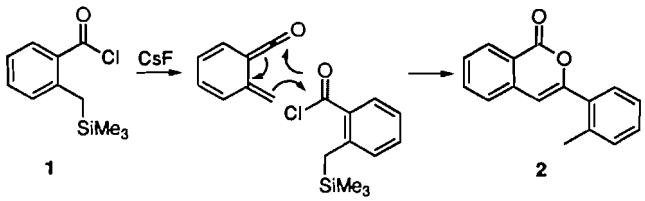
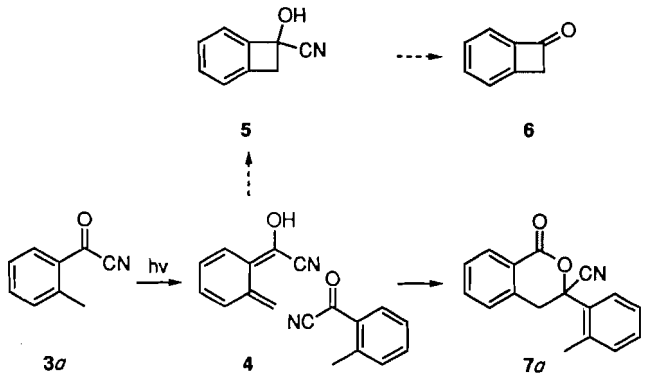
R. Connors,[2] E. Tran,[3] and T. Durst.[4] Ottawa-Carleton Chemistry Institute, Department of Chemistry, University of Ottawa, Ottawa, ON K1N 6N5, Canada.

[1] Revision received October 18, 1995.
[2] NSERCC post-graduate scholarship recipient, 1990–1992.
[3] NSERCC summer student, 1992.
[4] Author to whom correspondence may be addressed at: Department of Chemistry, University of Ottawa, Ottawa, Canada. Telephone: (613) 562-5800, ext. 6072. Fax: (613) 562-5170.

Scheme 1.



Scheme 2.



strated that photoenolization of **3***a*, in the presence of maleic anhydride, yields the expected cycloaddition product, confirming the intermediacy of **4** (9). Wagner (10) showed that substitution of the aldehydic hydrogen of 2-methylbenzaldehyde with either an alkyl or aryl group enhances benzocyclobutenol formation, presumably because of a greater propensity for cyclization by the sterically more crowded photoenol. Based on the possibility of a similar effect, we decided to reinvestigate the photochemsitry of **3***a*.

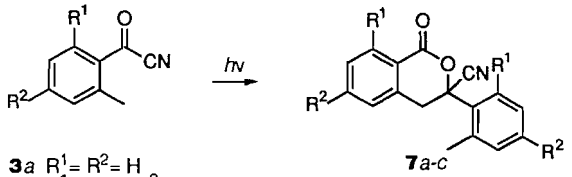
As was described in our preliminary communication (8), irradiation of 0.1–1.0 M acetonitrile solutions of **3***a* furnished an 80% yield of purified **7***a* (Scheme 2). Attempts to isolate the cyanohydrin **5** or the ketone **6** were unsuccessful, suggesting that **4** was not sterically crowded enough to facilitate benzocyclobutenol formation. The formation of **7***a* was interpreted as having resulted from the cycloaddition of **3***a* to photochemically generated **4**, followed by HCN loss.

The presence of the methoxy group in 2-methoxy-6-methylbenzaldehyde, while increasing steric crowding, is known to stabilize its photoenol by intramolecular hydrogen bonding, thus inhibiting benzocyclobutenol formation (11). Irradiation of compounds **3***b* and **3***c* in acetonitrile solution afforded the cycloadducts **7***b* and **7***c*, respectively, in excellent yields (Scheme 3). Photolysis of the *p*-methoxy analog **3***d* produced an intractable mixture. This was not altogether surprising since the similarly substituted aldehyde exhibits little useful photoactivity (12).

Compounds **3***b*–**3***d* were prepared from the appropriately substituted aldehydes (13) via a two-step sequence involving conversion to the TMS cyanohydrins (trimethylsilyl cyanide, ZnI_2), followed by oxidation (pyridinium dichromate) to the aroyl cyanides. The sequence was amenable to a one-pot procedure and afforded the desired compounds in approximately 60% overall yields from the requisite aldehydes.

The reaction between mixed aroyl cyanide pairs was also investigated. It was anticipated that benzoyl cyanide, being less sterically congested, should compete well with **3***a* as a

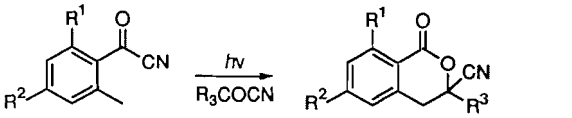
Scheme 3.



3*a* $R^1 = R^2 = H$
b R^1 = OMe R^2 = H
c R^1 = OMe R^2 = Me
d R^1 = H R^2 = OMe

7*a-c*

Scheme 4.



3*a* $R^1 = R^2 = H$
b R^1 = OMe R^2 = H
c R^1 = OMe R^2 = Me

8*a* $R^1 = R^2 = H$ R^3 = Ph
b R^1 = OMe R^2 = H R^3 = Ph
c R^1 = OMe R^2 = Me R^3 = Ph
d R^1 = OMe R^2 = H
R^3 = 2-MeO-4-MePh
e $R^1 = R^2 = H$ $R^3 = CH_3$

dienophile. Indeed, irradiation of an acetonitrile solution of **3***a*, in the presence of two equivalents of benzoyl cyanide, gave the cycloadduct **8***a* in 83% yield (Scheme 4); no trace of **7***a* was detected, even when only one equivalent of benzoyl cyanide was used. The aroyl cyanides **3***b* and **3***c* exhibited similar behavior when irradiated in the presence of benzoyl cyanide, furnishing the adducts **8***b* and **8***c* in excellent yield. Finally, the highly substituted cycloadduct **8***d* was prepared in 95% yield by irradiation of an acetonitrile solution of the 2,6-disubstituted benzoyl cyanide **3***b* in the presence of one equivalent of 2-methoxy-4-methylbenzoyl cyanide.

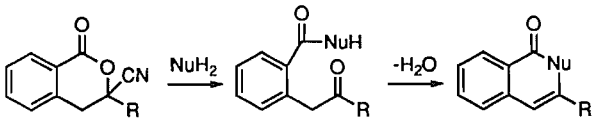
Cycloaddition between the cyanohydrin OQDMs and alkanoyl-substituted acylcyanides was also found to be highly efficient. For example, irradiation of 2-methylbenzoyl cyanide in the presence of 2 equivalents of acetyl cyanide afforded 50% of adduct **8***e*.

The cycloadducts **7** and **8** contain an interesting combination of functional groups, with the internally acylated cyanohydrin representing a masked carbonyl function that would be revealed by loss of HCN following ester cleavage (Scheme 5). Such a process would generate the intermediate **9**, which, depending on the nature of the nucleophile, would be able to undergo cyclization to a fused ring system. This process has been realized with nucleophiles such as methyllithium and various amines and resulted in the synthesis of highly functionalized 3-arylnaphthols and 3-substituted isoquinolones, respectively. Finally, treatment of the adducts **7** and **8** with strong bases afforded isocoumarins.

Preparation of 3-aryl-1-naphthols

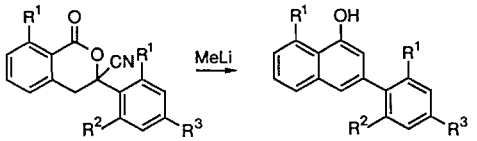
Treatment of a THF solution of **7***a* with 2 equivalents of methyllithium at −78°C and slowly warming the reaction mixture to room temperature gave the naphthol **10***a* in 60% yield (Scheme 6). Compound **7***b* was similarly converted, in 78% yield, into the naphthol **10***b*, which was readily characterized by its ^1H NMR spectrum showing the methyl group at δ = 2.30, singlets at δ = 6.78 and 7.36 ppm due to the C2 and C4 hydrogens on the naphthol ring, seven additional aromatic

Scheme 5.



7,8 9

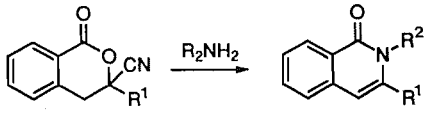
Scheme 6.



7*a* $R^1 = R^3 = H$ $R^2 = Me$
8*d* $R^1 = OMe$ $R^2 = H$ $R^3 = Me$

10*a* $R^1 = R^3 = H$ $R^2 = Me$
b $R^1 = OMe$ $R^2 = R^2 = H$ $R^3 = Me$

Scheme 7.



8*a* $R^1 = Ph$
e $R^1 = Me$

11*a* $R^1 = Ph$ $R^2 = Bn$
b $R^1 = Ph$ $R^2 = n$Bu
c $R^1 = Me$ $R^2 = Bn$
d $R^1 = Me$ $R^2 = n$Bu

Scheme 8.

8*a* R = Ph
e R = Me

12*a,b*

hydrogens, and a broad exchangeable singlet at 5.53 ppm corresponding to the phenolic hydrogen. Analysis of the ^{1}H NMR spectrum of the crude product indicated that complex mixtures consisting of a methyl ketone (compound **9**, NuH=CH_3, Scheme 5) and permethylated by-products were obtained when the same methodology was attempted with **7***c* and **7***d*. Presumably, the steric crowding in the 2,6-disubstituted biaryl adducts is sufficient to inhibit facile cyclization to the naphthols from the intermediate methyl ketones.

Isoquinolones and isocoumarins

In addition to the naphthols, the cycloadducts provided a facile route to various isoquinolones. The isoquinolone (1-oxo-1,2-dihydroisoquinoline) ring system is of interest owing to its presence in numerous alkaloids, in addition to its utility as a synthetic intermediate (14).

Compound **8***a* (Scheme 7), when refluxed with 1.5 equivalents of benzylamine in dry cyclohexane, yielded a viscous yellow oil that gave a complex proton NMR spectrum and exhibited a strong infrared absorbance at 1650 cm^{-1}. This material was readily converted to **11***a* (86%) upon further refluxing in 50% aqueous acetic acid. Compound **11***a* exhibited a strong infrared absorbance at 1652 cm^{-1}, confirming the presence of the amide functionality, as well as characteristic signals in the proton NMR spectrum at 5.23 and 6.43 ppm due to the benzyl and alkene hydrogens, respectively. The same methodology was applied to the synthesis of compounds **11***b–d* from **8***a* or **8***e* with yields ranging from 60 to 80%.

Finally, the potential for an isocoumarin synthesis was briefly investigated. The cycloadducts **8***a–e* are essentially masked isocoumarins that, it may be envisioned, have undergone addition of HCN across the 3,4 double bond. It follows that the isocoumarins should be accessible by base-catalyzed elimination of HCN. Initial attempts employing DBU or DBN, known to catalyze efficient dehydrohalogenation (15), gave unsatisfactory results with **8***a–e*. Potassium *tert*-butoxide proved to be the reagent of choice as treatment of an ice-cooled THF solution of compound **8***a* (Scheme 8) with 1.5 equivalents of the base yielded the known isocoumarin **12***a* (16) in 50% yield. Similarly, isocoumarin **12***b* (17) was prepared from **8***e* in 66% yield.

Experimental section

General

Melting points were determined by use of a Gallenkamp digital melting point apparatus and are uncorrected. IR spectra were recorded as chloroform solutions on a Bomem–Michelson MB-100 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained as $CHCl_3$ solutions on either a Varian XL-300 or a Gemini-200 spectrometer with the chemical shifts reported in ppm relative to TMS. Solvents for the extractions and chromatographic purifications (ethyl acetate = EA, and hexane = H) were routinely distilled prior to use. Reagent grade acetonitrile was used as received. Silica gel, 230–400 mesh, was used for flash chromatography.

2-Methylbenzoyl cyanide (*3a*) (**9**)

A mixture of 20 g (0.13 mol) of 2-methylbenzoyl chloride, 6.3 g (0.13 mol) sodium cyanide, and 0.1 g (0.36 mmol) of tetrabutylammonium chloride in 140 mL of 5:1 CH_2Cl_2–water was vigorously stirred at room temperature for 12 h, after which time IR analysis indicated complete reaction. After filtration of the solids the organic phase was separated, dried over magnesium sulfate, and concentrated in vacuo, giving 19.6 g of a yellow oil. Vacuum distillation furnished 11.3 g (60%) of a colorless liquid (bp 75–80°C/10 Torr; 1 Torr = 133.3 Pa) that solidified on standing. IR: 2222, 1680 cm^{-1}; ^{1}H NMR δ: 2.61 (s, 3H), 7.35 (d, 1H, *J*=7.5 Hz), 7.44 (dd, 1H, *J* = 7.5, 7.8 Hz), 7.60 (t, 1H, *J* = 7.5 Hz), 8.20 (d, 1H, *J* = 7.8 Hz); MS (EI) *m/z*: 145 (M^+), 118, 90.

2-Methoxy-6-methylbenzoyl cyanide (*3b*)

To an ice-cooled stirred solution of 5.0 g (33.3 mmol) of 2-methoxy-6-methylbenzaldehyde and 100 mg of zinc iodide (0.3 mmol) in 75 mL CH_2Cl_2 was added 3.6 g (4.9 mL, 36.7 mmol) of trimethylsilyl cyanide via syringe under nitrogen atmosphere. The mixture was allowed to warm to room temperature and TLC analysis (H/EA, 3:1) indicated complete conversion after 1 h after warming. The solvent was removed on a rotovap at 40°C and the concentrate passed through 20 g of 70–230 mesh silica gel with 150 mL of CH_2Cl_2. The CH_2Cl_2 solution of the TMS cyanohydrin was transferred to a

250 mL round-bottomed flask, cooled to 0°C under nitrogen atmosphere, and 18.8 g (50.0 mmol) of pyridinium dichromate was introduced, with efficient stirring, over 5 min. The mixture was stirred at room temperature for 12 h after which time the solvent was removed on a rotovap at 20°C. The residue was triturated with ether and the solution was filtered through 20 g 70–230 mesh silica gel. Concentration of the ether solution produced 4.2 g of crude **3*b***, which furnished 3.5 g (60%) of purified **3*b*** as yellow needles after flash chromatography (3:1 H/EA); mp 55.3–56.1°C (CH_2Cl_2–hexane); IR: 2220, 1670 cm^{-1}; ^1H NMR δ: 2.39 (s, 3H), 3.96 (s, 3H), 6.86 (d, 1H, J = 7.5 Hz), 6.87 (d, 1H, J = 8.3 Hz), 7.43 (t, 1H, J = 8.4 Hz); ^{13}C NMR δ: 20.7, 56.1, 109.7, 114.8, 123.2, 124.2, 135.5, 142.2, 161.1, 167.6; MS (EI) *m/z*: 175 (M^+), 160, 148; HRMS calcd. for $C_{10}H_9NO_2$: 175.0633; found: 175.0635.

2-Methoxy-4,6-dimethylbenzoyl cyanide (3*c*)

A solution of 5.0 g (33.3 mmol) of 2-methoxy-4,6-dimethylbenzaldehyde in 75 mL of CH_2Cl_2 was treated as described for **3*b***. Concentration of the product mixture followed by trituration with ether and filtration of the solution through a silica gel plug gave 5.6 g of a tan-brown solid. The crude aroyl cyanide was readily crystallized from CH_2Cl_2–hexane, furnishing 4.6 g (79%) of pure **3*c*** as yellow crystals, mp 71.8–72.5°C. IR: 2219, 1608 cm^{-1}; ^1H NMR δ: 2.34 (s, 3H), 2.35 (s, 3H), 3.93 (s, 3H), 6.65 (s, 1H), 6.66 (s, 1H); ^{13}C NMR δ: 21.0, 22.2 55.9, 110.4, 115.0, 120.6, 125.4, 142.6, 147.5, 161.5, 166.8; MS (EI) *m/z*: 189 (M^+), 174, 162; HRMS calcd. for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0802.

2-Methyl-4-methoxybenzoyl cyanide (3*d*)

A solution of 5.0 g (33.3 mmol) of 2-methyl-4-methoxybenzaldehyde in 75 mL of CH_2Cl_2 was treated as described for **3*b***. Concentration of the product mixture followed by trituration with ether and filtration of the solution through a silica gel plug gave 5.1 g of a yellow solid. The crude aroyl cyanide crystallized from ether–hexane, furnishing 4.5 g (78%) of pure **3*d*** as colorless needles, mp 62.0–62.8°C. IR: 2219, 1667 cm^{-1}; ^1H NMR δ: 2.59 (s, 3H), 3.90 (s, 3H), 6.79 (d, 1H, J = 2.0 Hz), 6.88 (dd, 1H, J = 2.0, 8.8 Hz), 8.15 (d, 1H, J = 8.8 Hz) ^{13}C NMR δ: 22.4, 55.7, 111.7, 113.6, 118.5, 124.9, 138.15, 146.0, 165.2, 166.6; MS (EI) *m/z*: 175 (M^+), 163, 148; HRMS calcd. for $C_{10}H_9NO_2$: 175.0633; found: 175.0648.

2-Methoxy-4-methylbenzoyl cyanide (3*e*)

A solution of 5.0 g (33.3 mmol) of 2-methoxy-4-methylbenzaldehyde in 75 mL of CH_2Cl_2 was treated as described for **3*b***. Flash chromatography (5:1 H/EA) gave 3.8 g (65%) **3*e*** as a yellow oil, which solidified on storage at 0°C (mp 68.2–69.0°C). IR: 2221, 1608 cm^{-1}; ^1H NMR δ: 2.42 (s, 3H), 3.96 (s, 3H), 6.81 (s, 1H), 6.87 (d, 1H, J = 8.1 Hz), 7.84 (d, 1H, J = 8.1 Hz); ^{13}C NMR δ: 22.5, 55.9, 112.9, 114.3, 120.2, 122.1, 132.9, 150.5, 161.3, 164.7; MS (EI) *m/z*: 175 (M^+), 158, 149; HRMS calcd. for $C_{10}H_9NO_2$: 175.0633; found: 175.0646.

3,4-Dihydro-3-cyano-3-(2-methylphenyl)-1*H*-2-benzopyran-1-one (7*a*)

A solution of 300 mg (2.1 mmol) of 2-methylbenzoyl cyanide in 2.0 mL of acetonitrile (1.0 M), contained in a quartz test tube, was suspended 10 cm from a Hanovia medium-pressure mercury lamp and irradiated until TLC analysis indicated complete conversion of the starting material (5–6 h). Concentration of the solvent on a rotovap at 40°C followed by flash chromatography (5:1 H/EA) of the crude adduct gave 220 mg (81%) of **7*a*** as white needles, mp 126.5–127.5°C (CH_2Cl_2–hexane); IR: 1747 cm^{-1}; ^1H NMR δ: 2.68 (s, 3H), 3.64 (d, 1H, J = 16.5 Hz), 3.75 (d, 1H, J = 16.5 Hz), 7.23–7.40 (m, 4H), 7.46–7.70 (m, 3H), 8.16 (d, 1H, J = 7.7 Hz); ^{13}C NMR δ: 20.9, 37.4, 77.4, 117.5, 123.7, 125.6, 126.4, 127.9, 129.0, 130.8, 130.8, 132.4, 133.1, 135.0, 135.6, 136.8, 162.0; MS (EI) *m/z*: 262 $(M-1)^+$, 245, 218; HRMS calcd. for $C_{17}H_{13}NO_2$: 263.0946; found: 263.0935.

3,4-Dihydro-3-cyano-8-methoxy-3-(2-methoxy-6-methylphenyl)-1*H*-2-benzopyran-1-one (7*b*)

A solution of 300 mg (1.7 mmol) of 2-methoxy-6-methylbenzoyl cyanide in 2.0 mL of acetonitrile, contained in a quartz test tube, was irradiated as described for **7*a*** until TLC analysis (H/EA acetate 2:1) indicated complete conversion of the starting material (12 h). Concentration of the solvent on a rotvap at 40°C followed by flash chromatography (CH_2Cl_2) of the crude adduct gave 249 mg (90%) of **7*b*** as a white solid. Recrystallization from CH_2Cl_2-hexane afforded colorless crystals, mp 145.3–146.0°C. IR: 1744 cm^{-1}; ^1H NMR δ: 2.61 (s, 3H), 3.46 (d, 1H, J = 16.9 Hz), 3.66 (d, 1H, J = 16.9 Hz), 3.87 (s, 3H), 3.94 (s, 3H), 6.85 (m, 3H), 6.98 (d, 1H, J = 8.3 Hz), 7.22 (dd, 1H, J = 7.8, 5.36 Hz), 7.53 (dd, 1H, J = 7.8, 8.3 Hz); ^{13}C NMR δ: 23.2, 38.2, 56.1, 56.2, 77.0 110.5, 111.9, 112.2, 118.2, 119.6, 122.4, 126.4, 130.0, 135.6, 138.2, 138.6, 156.4, 158.6, 161.4; MS (EI) *m/z*: 322 $(M-1)^+$, 278, 263; HRMS calcd. for $C_{19}H_{17}NO_4$: 323.1158; found: 323.1160.

3,4-Dihydro-3-cyano-8-methoxy-6-methyl-3-(2-methoxy-4,6-dimethylphenyl)-1*H*-2-benzopyran-1-one (7*c*)

A solution of 300 mg (1.6 mmol) of 2-methoxy-4,6-dimethylbenzoyl cyanide in 2.0 mL of acetonitrile was irradiated as above until TLC analysis indicated complete conversion of the starting material (16 h). Concentration of the solvent at 40°C followed by flash chromatography (2:1 H/EA) gave 140 mg (50%) of **7*c*** (colorless crystals from CH_2Cl_2–hexane), mp 202.5–203.0°C. IR: 1741 cm^{-1}; ^1H NMR δ: 2.28 (s, 3H), 2.38 (s, 3H), 2.56 (s, 3H), 3.40 (d, 1H, J = 16.6 Hz), 3.58 (d, 1H, J = 16.6 Hz), 3.85 (s, 3H), 3.93 (s, 3H), 6.65 (s, 2H), 6.67 (s, 1H), 6.76 (s, 1H); ^{13}C NMR δ: 21.2, 22.2, 23.0, 38.4, 56.1, 56.1, 77.4, 109.7, 111.3, 112.6, 118.4, 119.7, 120.5, 127.2, 137.9, 138.6, 140.1, 147.0, 156.4, 158.9, 161.4; MS (EI) *m/z*: 351 (M^+), 350, 306; HRMS calcd. for $C_{21}H_{21}NO_4$: 351.1471; found 351.1466.

3,4-dihydro-3-cyano-3-phenyl-1*H*-2-benzopyran-1-one (8*a*)

A solution of 300 mg (2.1 mmol) of 2-methylbenzoyl cyanide and 550 mg (4.1 mmol) of benzoyl cyanide in 2.0 mL of acetonitrile was irradiated as described above for 6 h. Concentration of the solvent on a rotovap at 40°C followed by flash chromatography (5:1 H/EA) of the crude adduct gave 385 mg (75%) of **8*a***, colorless plates, mp 144.6–146.1°C, from ether–hexane. IR: 1748 cm^{-1}; ^1H NMR δ: 3.48 (d, 1H, J = 16.7 Hz), 3.60 d, 1H, J = 16.7 Hz), 7.34 (d, 1H, J = 7.5 Hz), 7.45–7.55 (m, 4H), 7.61–7.71 (m, 3H), 8.19 (d, 1H, J = s7.7 Hz); ^{13}C NMR δ: 40.8, 78.2, 117.8, 123.6, 125.1, 127.7, 129.0, 129.2,

130.1, 130.9, 135.0, 135.5, 135.7, 162.2; MS (EI) *m/z*: 249 (M^+), 203, 190; HRMS calcd. for $C_{16}H_{11}NO_2$: 249.07900; found: 249.0809.

3,4-Dihydro-3-cyano-8-methoxy-3-phenyl-1*H*-2-benzopyran-1-one (8*b*)

A solution of 300 mg (1.7 mmol) of 2-methoxy-6-methylbenzoyl cyanide and 450 mg (3.4 mmol) of benzoyl cyanide in 2.0 mL of acetonitrile was irradiated as above for 6 h. Concentration of the solvent followed by flash chromatography (3:1 H/EA) of the crude adduct gave 420 mg (88%) of **8*b*** as a white solid, mp 146.0–147.0°C. IR: 1748 cm^{-1}; ^1H NMR δ: 3.40 (d, 1H, J = 16.4 Hz), 3.46 (d, 1H, J = 16.4 Hz), 3.98 (s, 3H), 6.87 (d, 1H, J = 7.6 Hz), 7.02 (d, 1H, J = 8.6 Hz), 7.40–7.50 (m, 3H), 7.57 (t, 1H, J = 7.6 Hz), 7.65–7.75 (m, 2H); ^{13}C NMR δ: 41.2, 56.3, 77.5, 112.0, 112.3, 117.8, 119.6, 125.1, 129.1, 130.0, 135.7, 135.9, 138.0, 158.8, 161.6; MS (EI) *m/z*: 279 (M^+), 249, 220; HRMS calcd. for $C_{17}H_{13}NO_3$: 279.0895; found: 279.0888.

3,4-Dihydro-3-cyano-8-methoxy-6-methyl-3-phenyl-1*H*-2-benzopyran-1-one (8*c*)

A solution of 300 mg (1.6 mmol) of 2-methoxy-4,6-dimethylbenzoyl cyanide and 420 mg (3.2 mmol) of benzoyl cyanide in 2.0 mL of acetonitrile was irradiated as above for 6 h. Concentration of the solvent followed by flash chromatography (5:1 H/EA) gave 363 mg (78%) of **8*c***, white solid, mp 166.0–167.0°C. IR: 1746 cm^{-1}; ^1H NMR δ: 2.41 (s, 3H), 3.33 (d, 1H, J = 16.1 Hz), 3.47 (d, 1H, J = 16.1 Hz), 3.97 (s, 3H), 6.69 (s, 1H), 6.82 (s, 1H), 7.50 (m, 3H), 7.70 (m, 2H); ^{13}C NMR δ: 22.3, 41.2, 56.2, 77.4, 109.4, 112.9, 117.9, 120.4, 125.1 129.0, 129.9, 135.8 137.8, 147.6 159.0, 161.8; MS (EI) *m/z*: 293 (M^+), 263, 247; HRMS calcd. for $C_{18}H_{15}NO_3$: 293.1052; found: 293.1055.

3,4-Dihydro-3-cyano-8-methoxy-3-(2-methoxy-4-methylphenyl)-1*H*-2-benzopyran-1-one (8*d*)

A solution of 300 mg (1.7 mmol) of 2-methoxy-6-methylbenzoyl cyanide and 300 mg (1.7 mmol) of 2-methoxy-4-methylbenzoyl cyanide in 2.0 mL of acetonitrile contained in a quartz test tube was irradiated for 6 h after which time TLC analysis indicated complete conversion of the starting materials. Concentration of the solvent at 40°C followed by flash chromatography (2:1 H/EA acetate) of the crude adduct gave 526 mg (95 %) of **8*d*** as a yellow solid, mp 176.5–177.5°C. IR: 1745 cm^{-1}; ^1H NMR δ: 2.36 (s, 3H), 3.34 (d, 1H, J = 16.3 Hz), 3.78 (d, 1H, J = 16.3 Hz), 3.91 (s, 3H), 3.96 (s, 3H), 6.84 (m, 3H), 6.98 (d, 1H, J = 8.5 Hz), 7.53 (dd, 1H, J = 7.8, 7.6), 7.60 (d, 1H, J = 7.9 Hz); ^{13}C NMR δ: 21.5, 38.2, 55.9, 56.2, 77.4, 111.9, 112.3, 112.9, 117.6, 119.7, 121.0, 121.7, 126.1, 135.7, 138.6, 141.5, 155.8, 159.1, 161.4; MS (EI) *m/z*: 323 (M^+), 293, 278; HRMS calcd. for $C_{19}H_{17}NO_4$: 323.1158; found: 323.1161.

3,4-Dihydro-3-cyano-3-methyl-1*H*-2-benzopyran-1-one (8*e*)

A solution of 300 mg (2.1 mmol) of 2-methylbenzoyl cyanide and 285 mg (4.1 mmol) of acetyl cyanide in 2.0 mL of acetonitrile was irradiated as described above until TLC analysis indicated complete conversion of the starting material (12 h). Concentration of the solvent followed by flash chromatography (3:1 H/EA) gave 192 mg (50%) of **8*e*** as a white solid, mp 98.0–100.0°C. IR: 1746 cm^{-1}; ^1H NMR δ: 1.94 (s, 3H), 3.26 (d, 1H, J = 16.6 Hz), 3.32 (d, 1H, J = 16.6 Hz) 7.29 (d, 1H, J = 6.8 Hz), 7.48 (t, 1H, J = 6.4 Hz), 7.63 (dt, 1H, J = 1.4, 7.5 Hz), 8.12 (dd, 1H, J = 14, 7.5 Hz); ^{13}C NMR δ: 26.6, 38.26 (t), 77.4, 118.8, 123.34 (s), 127.6, 128.9, 130.89, 134.89, 135.4, 162.3; MS (EI) *m/z*: 187 (M^+), 172, 144; HRMS calcd. for $C_{11}H_9NO_2$: 187.0633; found: 187.0646

3-(2-Methylphenyl)-1-naphthol (10*a*)

To a stirred THF solution of 600 mg (2.3 mmol) of 3,4-dihydro-3-cyano-3-(2-methylphenyl)-1*H*-2-benzopyran-1-one (**8*a***), cooled to −78°C under nitrogen atmosphere, was added via syringe 1.8 mL (2.5 mmol) of MeLi (1.4 M in ether). The mixture was maintained at −78°C for 30 min before a second 1.8 mL aliquot of MeLi was administered. The reaction mixture was then warmed to room temperature over 30 min and left stirring overnight (15 h). The yellow solution was quenched by dropwise addition of 10% aqueous HCl and the resulting phases were separated. The aqueous layer was extracted with ether and the combined organic phases were washed with brine. The resulting ether solution was dried over $MgSO_4$ and concentrated on a rotvap, giving 412 mg of a brown oil. Flash chromatography (1:2 H/CH_2Cl_2) furnished 320 mg (60%) of **10*a*** as a brown oil. IR: 3577 cm^{-1}; ^1H NMR δ: 2.30 (s, 3H), 5.53 (s, 1H), 6.78 (s, 1H), 7.28 (s, 4H), 7.36 (s, 1H), 7.50 (m, 2H), 7.82 (m, 1H), 8.20 (m, 1H); ^{13}C NMR δ: 20.6, 110.9, 120.6, 121.5, 123.3, 125.1, 125.7, 126.7, 127.3, 127.7, 129.77 (d), 130.3, 134.5, 135.5, 139.7, 141.7, 151.0; MS (EI) *m/z*: 234 (M^+), 215, 202; HRMS calcd. for $C_{17}H_{14}O$: 234.1045; found: 234.1043.

8-Methoxy-3-(2-methoxy-4-methylphenyl)-naphthol (10*b*)

3,4-Dihydro-3-cyano-8-methoxy-3-(2-methoxy-4-methylphenyl)-1*H*-2-benzopyran-1-one (**8*d***) (100 mg; 0.3 mmol) was treated as described above for **10*a***, giving 108 mg of a brown oil. Flash chromatography (3:1 H/EA) furnished 78 mg (86%) of **10*b*** as a yellow oil. IR: 3404 cm^{-1}; ^1H NMR δ: 2.40 (s, 3H), 3.80 (s, 3H), 4.04 (s, 3H), 6.73 (d, 1H, J = 7.7 Hz), 6.81 (s, 1H), 6.85 (d, 1H, J = 8.4 Hz), 7.10 (d, 1H, J = 1.5 Hz), 7.27 (t, 2H, J = 7.6 Hz), 7.40 (d, 1H, J = 6.2 Hz), 7.42 (d, 1H, J = 1.6 Hz), 9.27 (s, 1H); ^{13}C NMR δ: 21.5, 55.5, 56.1, 103.7, 112.2, 112.4, 113.9, 119.3, 121.4, 122.1, 125.5, 127.4, 130.7, 136.6, 138.2, 138.9, 153.6, 156.0, 156.4; MS (EI) *m/z*: 294 (M^+), 267, 234; HRMS calcd. for $C_{19}H_{18}O_3$: 294.1256; found: 294.1264.

1-Oxo-3-phenyl-2-phenylmethyl-1,2-dihydroisoquinoline (11*a*)

A solution of 200 mg (0.8 mmol) of 3,4-dihydro-3-cyano-3-phenyl-1*H*-2-benzopyran-1-one (**8*a***) and 130 mg (1.2 mmol) benzylamine in 10 mL cyclohexane was heated to reflux for 15 h after which time TLC analysis indicated complete conversion of the starting materials. The solvent was removed on a rotovap, the concentrate dissolved in 10 mL 50% aqueous acetic acid, and the mixture heated to reflux for an additional 3 h. After cooling to room temperature, the product mixture was diluted with 20 mL water and extracted with three 15 mL portions of CH_2C1_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated, giving a yellow oil that after flash chromatography (3:1 H/EA) furnished 217 mg (86%) of **11*a***. IR: 1652 cm^{-1}; ^1H NMR δ: 5.23 (s, 2H), 6.43 (s, 1H), 6.88 (m, 2H), 7.14–7.70 (m, 11H), 8.48 (d, 1H, J = 8.0

Hz); ^{13}C NMR δ: 48.5, 108.0, 125.2, 125.8, 126.7, 126.8, 126.9, 128.2, 128.2, 128.3, 128.8, 129.1, 132.5, 135.8, 136.4, 137.6, 143.8, 163.1; MS (EI) *m/z*: 310 $(M-1)^+$, 232, 205; HRMS calcd. for $C_{22}H_{17}NO$: 311.1310; found: 311.1287.

2-Butyl-1-oxo-3-phenyl-1,2-dihydroisoquinoline (11*b*)

A solution of 275 mg (1.1 mmol) of 3,4-dihydro-3-cyano-3-phenyl-1*H*-2-benzopyran-1-one (**8*a***) and 120 mg (1.7 mmol) of *n*-butylamine in 15 mL cyclohexane was treated as described for **11*a***. Flash chromatography (3:1 H/EA) gave 236 mg (77%) of **11*b*** IR: 1648 cm^{-1}; ^{1}H NMR δ: 0.70 (t, 3H, J = 7.4 Hz), 1.11 (m, 2H), 1.52 (m, 2H), 3.92 (t, 2H, J = 7.7 Hz), 6.37 (s, 1H), 7.40 (m, 7H), 7.60 (t, 1H, J = 7.4 Hz); ^{13}C NMR δ: 13.4, 19.9, 30.7, 45.3, 107.7, 125.2, 125.6, 126.5, 127.9, 128.3, 128.8, 129.0, 132.2, 136.2, 136.2, 143.6, 162.7; MS (EI) *m/z*: 277 (M^+), 260, 234, 221; HRMS calcd. for $C_{19}H_{19}NO$: 277.1426; found: 277.1446.

1-Oxo-3-methyl-2-phenylmethyl-1,2-dihydroisoquinoline (11*c*)

A solution of 217 mg (1.2 mmol) of 3,4-dihydro-3-cyano-3-methyl-1*H*-2-benzopyran-1-one (**8*e***) and 200 mg (1.8 mmol) benzylamine in 15 mL cyclohexane was treated as described for **11*a***. Flash chromatography (4:1 H/EA) gave 165 mg (57%) of **11*c***: IR: 1657 cm^{-1}; ^{1}H NMR δ: 2.30 (s, 3H), 5.40 (s, 2H), 6.34 (s, 1H), 7.13 (d, 2H, J = 7.6 Hz), 7.23 (m, 3H), 7.41 (m, 2H), 7.59 (t, 1H, J = 7.5 Hz), 8.41 (d, 1H, J = 8.1 Hz); ^{13}C NMR δ: 20.6, 47.0, 106.1, 124.4, 125.0, 125.9, 126.3, 127.1, 128.2, 128.7, 132.3, 136.8, 137.6, 139.5, 163.4; MS (EI) *m/z*: 249 (M^+), 232, 172, 158; HRMS calcd. for $C_{17}H_{15}NO$: 249.1154; found: 249.1161.

2-Butyl-1-oxo-3-methyl-1,2-dihydroisoquinoline (11*d*)

A solution of 289 mg (1.5 mmol) of 3,4-dihydro-3-cyano-3-methyl-1*H*-2-benzopyran-1-one (**8*e***) and 210 mg (2.3 mmol) of *n*-butylamine in 15 mL cyclohexane was treated as described for **11*a***. Flash chromatography (4:1 H/EA) gave 281 mg (85%) of **11*d***: IR: 1651 cm^{-1}; ^{1}H NMR δ: 0.92 (t, 3H, J = 7.2 Hz), 1.41 (m, 2H), 1.64 (m, 2H), 2.35 (s, 3H), 2.35 (s, 3H), 4.01 (t, 2H, J = 7.7 Hz), 6.25 (s, 1H), 7.33 (m, 2H), 7.50 (t, 1H, J = 8.3 Hz), 8.31 (d, 1H, J = 8.1 Hz); ^{13}C NMR δ: 13.7, 20.3, 20.4, 30.9, 44.1, 105.9, 124.5, 124.8, 125.7, 127.8, 132.0., 136.6, 138.9, 162; MS (EI) *m/z*: 215 (M^+), 198, 186, 173; HRMS calcd. for $C_{14}H_{17}NO$: 215.1310; found: 215.1298.

3-Phenyl-1*H*-2-benzopyran-1-one (12*a*)

To a stirred solution of 100 mg (0.4 mmol) of 3,4-dihydro-3-cyano-3-phenyl-1*H*-2-benzopyran-1-one (**8*a***) in 15 mL of dry THF, cooled to 0°C, was added 70 mg (0.6 mmol) of potassium *tert*-butoxide under nitrogen atmosphere. The mixture was warmed to room temperature and stirred for 15 h after which time TLC analysis indicated complete conversion of the starting material. The reaction was quenched by dropwise addition of 6.0 mL 10% aqueous HCL followed by extraction with three 15 mL aliquots of CH_2C1_2. After drying over $MgSO_4$ and concentrating the solvent, the crude isocoumarin was purified by flash cohromatography (4:1 H/EA) to give 45 mg (50%) of **12*a***, mp 89–90°C. The spectral properties agreed with the literature values (16).

3-Methyl-1*H*-2-benzopyran-1-one (12*b*)

A stirred solution of 100 mg (0.5 mmol) of 3,4-dihydro-3-cyano-3-methyl-1*H*-2-benzopyran-1-one (**8*e***) in 15 mL dry THF was treated as described above and gave 57 mg (66%) of purified **12*b***, mp 74°C, after flash chromatography (CH_2Cl_2). The melting point and spectral characteristics agreed with the literature values (17).

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