A Rare Acid-Promoted Elimination of *O*-Methyl Oximes: A Practical Synthesis of 3-Cyano-4-benzopyrones

Richard P. Hsung,* Craig A. Zificsak, Lin-Li Wei, Luke R. Zehnder, Francis Park,[1] Michelle Kim,[1] and Thuy-Trang T. Tran[1]

Department of Chemistry, The University of Minnesota, Minneapolis, Minnesota 55455

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Our interest in natural products containing the oxadecalin structural unit has led us to investigate [4 + 2] cycloaddition reactions involving 4-pyrones as dienophiles (**1** → **2** in Figure 1).[2−5] Such a strategy should serve as a highly convergent approach to the synthesis of natural products such as arisugacin (**3** in Figure 1),[4,6−8] pyripyropenes,[9] and forskolin.[10] However, at this point, a strong electron-withdrawing group has proven to be essential for rendering the electron-rich 4-pyrones as reactive dienophiles in these cycloadditions under thermal or Lewis acidic conditions.[3b,5a] Although this specific necessity could hinder the synthetic scope of this strategy, given the scarce studies of reactions using 4-pyrones as dienophiles, these initial endeavors have yielded interesting synthetic structures that could serve as entries to unique natural products and their analogues.

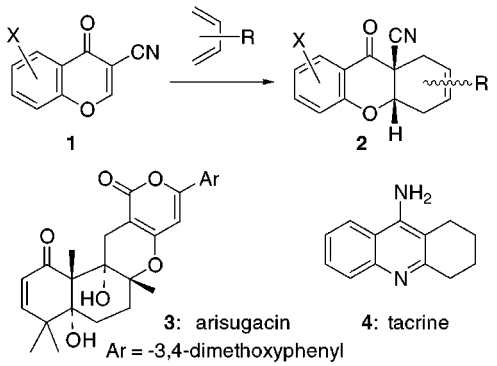

Figure 1.

Specifically, we have prepared an array of tetrahydroxanthone derivatives (**2**) via [4 + 2] cycloaddition reactions using 3-cyano-4-benzopyrones as dienophiles.[4a−b,11] These tetrahydroxanthone derivatives were evaluated for their anticholinesterase potential[11] because of the structural resemblance to tacrine (**4**, Cognex),[12] one of only three available therapeutics for antidementia diseases. More significantly, 4-benzopyrone derivatives are known for their pharmacological potential as antibacterial, antitumor, and antiallergy agents,[13] and recently, there have been reports indicating their prospects in demonstrating anti-HIV activity.[14] Given these synthetic and medicinal interests, useful preparations of various 4-benzopyrone derivatives can be significant. We here report a practical synthesis of 3-cyano-4-benzopyrone derivatives via an acid-promoted elimination of the corresponding *O*-methyl oximes.

We began our synthesis of 3-cyano-benzopyrones by focusing on a few reported procedures describing preparations from the corresponding aldehydes through oxime intermediates.[15] As shown in Scheme 1, when 3-formyl-4-benzopyrone **5** is refluxed with H_2NOH−HCl and a catalytic amount of concentrated HCl in 95% EtOH, the corresponding oxime **6** should be formed and undergo facile dehydration to provide 3-cyano-4-benzopyrone **8**. However, we were not able to isolate any desired 3-cyano-4-benzopyrones **8** in synthetically useful yields (yield ≤ 2−3%) under these conditions, nor were we able to intercept the corresponding oxime intermediate **6**. We

(1) UMN Undergraduate Research Participants: 1997−1999.

(2) For a recent review see: (a) Ghosh, C. K.; Ghosh, C. *Indian J. Chem.* **1997**, 968. For the first example of 3-acyl-4-pyrones functioning as dienophiles see: (b) Groundwater, P. W.; Hibbs, D. E.; Hursthouse, M. B.; Nyerges, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 163.

(3) For a recent elegant study on 3-acyl- and 3-cyano-4-pyrones functioning as dienophiles see: Chen, D.; Wang, J.; Totah, N. I. *J. Org. Chem.* **1999**, *64*, 1776.

(4) For studies on 3-nitrile-4-benzopyrones functioning as dienophiles see: (a) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904. (b) Hsung, R. P. *Heterocycles* **1998**, *48*, 421. (c) Granum, K. G.; Merkel, G.; Mulder, J. A.; Debbins, S. A.; Hsung, R. P. *Tetrahedron Lett.* **1998**, 9597.

(5) For the only other examples of benzopyrones functioning as dienophiles see: (a) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *13*, 3075. (b) Ohkata, K.; Kubo, T.; Miyamoto, K.; Ono, M.; Yamamoto, J.; Akiba, K. *Heterocycles* **1994**, *38*, 1483.

(6) Arisugacin has been found to be a potent and selective inhibitor of acetylcholinesterase. For a leading reference see: Otoguro, K.; Kuno, F.; Ōmura, S. *Pharmacol. Ther.* **1997**, *76*, 45.

(7) For studies related to arisugacin see: (a) Obata, R.; Sunazuka, T.; Tian, Z.; Tomoda, H.; Harigaya, Y.; Ōmura, S.; Smith, A. B. III. *Chem. Lett.* **1997**, 935. (b) Hua, D. H.; Chen, Y.; Sin, H.-S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J.-P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888.

(8) For our other related efforts see: (a) Hsung, R. P.; Shen, H. C.; Douglas, C. J.; Morgan, C. D.; Degen, S. J.; Yao, L. J. *J. Org. Chem.* **1999**, *64*, 690. (b) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Douglas, C. J.; McLaughlin, M. J.; Mulder, J. A.; Yao, L. J. *Org. Lett.* **1999**, *1*, 509. (c) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, 6903. (d) Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237−1240. (e) Douglas, C. J.; Sklenicka, H. M.; Shen, H. C.; Mathias, D. S.; Golding, G. M.; Hsung, R. P.; Degen, S. J.; Morgan, C. D.; Mueller, K. L.; Seurer, L. M.; Shih, R. A. *Tetrahedron* **1999**, *55*, in press.

(9) For leading references see: (a) Obata, R.; Sunazuka, T.; Li, Z. R.; Tian, Z. M.; Harigava, Y.; Tabata, N.; Tomoda, H.; Ōmura, S. *J. Antibiot.* **1996**, *49*, 1133. (b) Smith, A. B., III; Kinsho, T.; Sunazuka, T.; Ōmura, S. *Tetrahedron Lett.* **1996**, 6461. (c) Nagamitsu, T.; Sunazuka, T.; Obata, R.; Tomoda, H.; Tanaka, H.; Harigaya, Y.; Ōmura, S.; Smith, A. B., III. *J. Org. Chem.* **1995**, *60*, 8126. (d) Parker, K. A.; Resnick, L. *J. Org. Chem.* **1995**, *60*, 5726.

(10) For total syntheses of forskolin see: (a) Corey, E. J.; Jardine, P. D. S.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672. (b) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115.

(11) Degen, S. J.; Mueller, K. L.; Shen, H. C.; Mulder, J. A.; Golding, G. M.; Wei, L.-L.; Zificsak, C. A.; Hsung, R. P. *Bioorg. Med. Chem. Lett.* **1999**, 973.

(12) Summers, W. K.; Majovski, L. V.; Marsh, G. M.; Tachiki, K.; Kling, A. *N. Engl. J. Med.* **1986**, *315*, 1241.

(13) For some examples see: (a) Grinberg, L. N.; Newmark, H.; Kitrossky, N.; Rahamim, E.; Chevion, M.; Rachmilewitz, E. A. *Biochem. Pharmacol.* **1997**, *54*, 973. (b) Leanderson, P.; Faresjö, A. O.; Tagesson, C. *Free Radical Biol. Med.* **1997**, *23*, 235. (c) Agullo, G.; Payrastre, L. G.; Manenti, S.; Viala, C.; Résmésy, C.; Chap, H.; Payraste, B. *Biochem. Pharmacol.* **1997**, *53*, 1649. (d) Fotsis, T.; Pepper, M. S.; Aktas, E.; Breit, S.; Rasku, S.; Adlercreutz, H.; Wähälä, K.; Montesano, R.; Scheweigerer, L. *Cancer Res.* **1997**, *57*, 2916. (e) Wright, J. S.; Carpenter, D. J.; McKay, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4245.

(14) (a) Mahmood, N.; Piacent, S.; Pizza, C.; Burke, A.; Khan, A. I.; Hay, A. J. *Biochem. Biophys. Res. Commun.* **1996**, *229*, 73. (b) Li, B. Q.; Fu, T.; Yan, Y. D.; Baylor, N. W.; Ruscetti, F. W.; Kung, H. F. *Cell. Mol. Biol. Res.* **1993**, *39*, 119.

(15) (a) Nohara, A. *Tetrahedron Lett.* **1974**, 1187. (b) Nohara, A.; Umetani, T.; Sanno, Y. *Tetrahedron Lett.* **1973**, 1995. (c) Goerlitzer, K.; Dehne, A. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 448.

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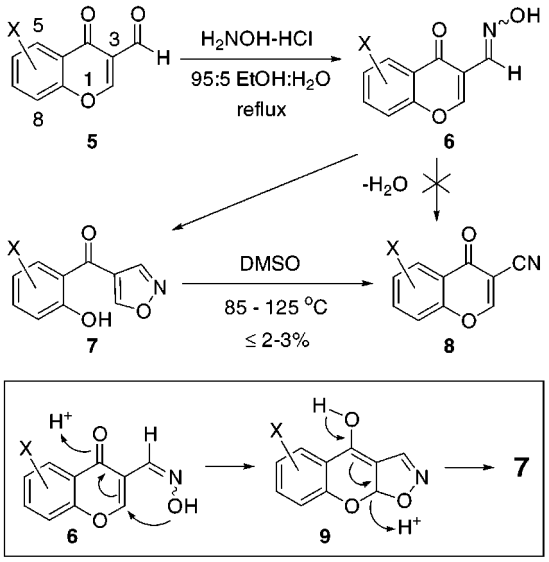
Scheme 1

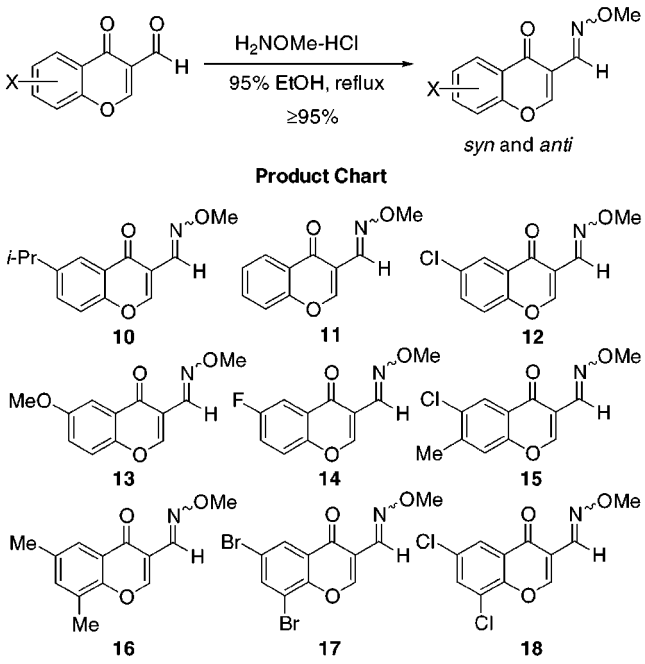


did, however, isolate the isoxazole **7**, in most cases as off-white solids that are completely insoluble in most organic solvents except DMSO and EtOH.

The isoxazole **7** has been reported but only as a minor product,[15] and given the aromatic nature of isoxazole, its formation could be readily rationalized as shown in Scheme 1. Nevertheless, as suggested by the reported procedures,[15a] these isoxazoles (**7**) were heated in DMSO[16] at 85 °C in an attempt to crack open the aromatic isoxazole ring and force the reaction pathway towards the desired 3-cyano-4-benzopyrones (**8**). These efforts also failed in leading to the desired 3-cyano-4-benzopyrones (**8**) in significant yields after taxing chromatographic purifications. Although we did manage a 67% yield on one occasion (X = 6,8-dimethyl), this effort was not again repeated.

Since literature procedures proved to be unsuccessful in our hands, we turned our attention to a variety of other approaches for the synthesis of nitriles.[17] For example, various oxidations of *N*,*N*-dimethylhydrazone derivatives with *m*-CPBA or MMPP in an attempt to eliminate *N*-oxide intermediates (a Cope-like elimination) afforded the desired 3-cyano-4-benzopyrones in very low yields.[18] We also tried to use base-promoted elimination of tosylimines and were met with difficulties, especially in preparations of tosylimines.[19] In addition, we attempted to prepare these 3-cyano-4-benzopyrones using palladium-catalyzed cross-coupling reactions, but these preliminary studies were also unsuccessful.[20,21]

Scheme 2



By examining the formation of isoxazole (**6** → **9** → **7** in Scheme 1), we became aware that if the proposed mechanistic pathway to the isoxazole is feasible, then the key is to prevent its formation by blocking the hydroxyl group. Although it was not possible to isolate the oxime intermediates (**6**), *O*-alkyl oximes may be isolated in this scenario because the initial cyclization could be arrested. As shown in Scheme 2, when 3-formyl-4-benzopyrones were refluxed in 95% EtOH in the presence of $H_2NOMe-HCl$ and a catalytic amount of concentrated HCl, a variety of desired *O*-methyl oximes **10**−**18** were isolated quantitatively as a mixture of *syn* and *anti* isomers (~2:1 ratio in favor of the *anti* isomer). Although the *syn* and *anti* isomers of these *O*-methyl oximes could be separated, such separations were not pursued because we were interested in the synthesis of nitrile compounds.

Various elimination conditions were examined in the attempt to prepare 3-cyano-4-benzopyrones from these *O*-methyl oximes. Although there are ample precedents for nitrile synthesis from *O*-alkyl oximes, it is surprising to find that most of these involve either base-induced elimination[22] or thermal elimination at an extremely high temperature.[23,24] There are essentially no examples of an acid-promoted elimination of *O*-methyl oximes. Because base-induced elimination was not successful,[25] a range of acids such as *p*-TsOH, CSA, TFA, HCl, and HNO_3 were examined using various solvents and temperatures. The

(16) Both anhydrous and wet DMSO were used, but neither condition was fruitful.

(17) For a review see: Falbe, J.; Bauer, W. In *Methoden Der Organischen Chemie (Houben-Weyl)*; Erweiterungs-u. Folgebd. zur 4. Aufl., Bd.E5. Georg Thieme: Stuttgart, New York, 1985; pp 1322−1371.

(18) (a) Mlochowski, J.; Giurg, M.; Uher, M.; Korenova, A.; Vegh, D. *J. Prakt. Chem.* **1996**, *338*, 65. (b) Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Liera, J.-M.; Vázquez, J. *Tetrahedron Lett.* **1993**, 141. (c) Díez, E.; Fernández, R.; Gasch, C.; Lassaletta, J.-M.; Liera, J.-M.; Martín-Zamora, E.; Vázquez, J. *J. Org. Chem.* **1997**, *62*, 5144.

(19) Glover, E. E.; Rowbottom, K. T. *J. Chem. Soc., Perkin Trans. 1* **1976**, 367.

(20) 3-Bromo- or 3-iodo-4-benzopyrone was reacted with KCN, CuCN, or NaCN under a series of palladium-catalyzed coupling conditions, but the only discernible product has been the homo-coupling product. Regeuiro-Ren, A.; Zificsak, C. A.; Hsung, R. P. Unpublished results.

(21) (a) Shiao, M.-J.; Shyu, L.-M.; Chen, C.-F. *Heterocycles* **1990**, *31*, 523. (b) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224.

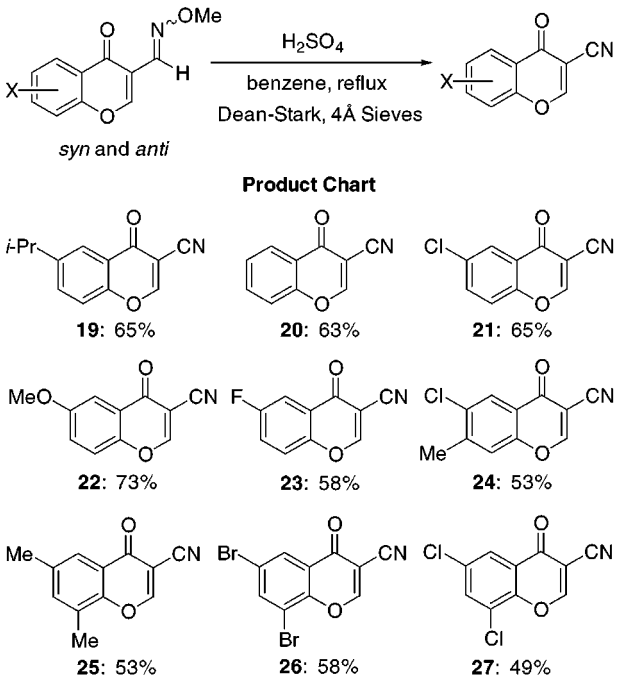
(22) For examples of base-promoted elimination of *O*-methyl oximes see: (a) Hegarty, A. F.; Tuohey, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1313. (b) Itsuno, S.; Miyazaki, K.; Ito, K. *Tetrahedron* **1986**, *27*, 3033.

(23) For examples of thermal elimination of *O*-methyl oximes see: (a) Hickson, C. L.; McNab, H. *J. Chem. Soc. Perkin Trans. 1* **1984**, 1569. (b) Leardini, R.; Mcnab, H.; Nanni, D.; Parsons, S.; Reed, D.; Tenan, A. G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1833.

(24) For an example of photochemically induced elimination of *O*-methyl oximes see: Pratt, A. C.; Abdul- Majid, Q. *J. Chem. Soc., Perkin Trans. 1* **1987**, 359.

(25) These *O*-methyl oximes were not very stable under basic conditions.

Scheme 3

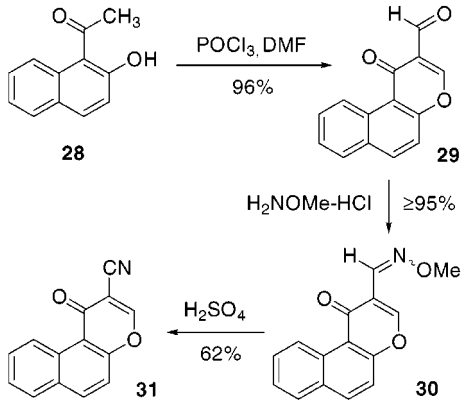


optimized condition would eventually involve refluxing a benzene solution of an appropriate *O*-methyl oxime in the presence of 195.0−240.0 mg (100.0−130.0 μL) of concentrated H_2SO_4 per 1.0 mmol of the starting *O*-methyl oxime and a Dean−Stark trap packed with 4 Å sieves to trap out the methanol (Scheme 3).

The reaction progress should be monitored closely by TLC. It was found that prolonged refluxing can reduce the yield significantly because a slow decomposition of the nitrile product did occur under these conditions. These reactions were routinely terminated when there were still small amounts of starting materials left. Hence, isolated yields for these elimination reactions were consistently within the range of 45%−75% depending upon the termination point. Nevertheless, we were able to achieve preparations of 3-cyano-4-benzopyrones **19**−**27** (Scheme 3) through this protocol in a consistent manner. Both *syn* and *anti* isomers of *O*-methyl oximes undergo this acid-promoted elimination with relatively similar ease.

Given this preparation of 3-cyano-4-benzopyrones from 3-formyl-4-benzopyrones via the corresponding *O*-methyl oxime derivatives, it is then possible to construct many 3-cyano-4-benzopyrones with various substitution patterns on the aromatic ring because the starting 3-formyl-4-benzopyrones can be readily prepared from available hydroxyacetophenones.[15b] As shown in Scheme 4, the starting 2′-hydroxy-1′-acetonaphthone could be converted into the 3-formyl-4-naphthopyrone **29** in 96% yield under the Vilsmeier conditions. Following another quantitative formation of the *O*-methyl oxime **30**, the desired 3-cyano-4-naphthopyrone **31** was obtained in 62% yield under the elimination conditions described above and 86% yield based on recovered starting material. The compound **31** is an important intermediate to a class of therapeutics that exhibit potent antiallergic activity.[26]

Scheme 4



We have described here a practical synthesis of a variety of substituted 3-cyano-4-benzopyrones. Given the synthetic and medicinal interest of these compounds, this preparation should be significant in future studies utilizing these 4-benzopyrone derivatives as dienophiles for [4 + 2] cycloaddition reactions.

Experimental Section

All reagents were obtained from commercial suppliers and used without further purification unless otherwise indicated. DMF and benzene were distilled from calcium hydride (CaH_2) under nitrogen. The thin-layer chromatography (TLC) analysis was done using EM Science silica gel-60 plates (0.25 mm in thickness) with F254 as the fluorescence indicator. The eluted plates were developed under UV detector and/or stained with either an aqueous solution of potassium permanganate ($KMnO_4$) or an alcoholic solution of phosphomolybdic acid (PMA). Chromatographic purifications were performed on EM Science silica gel (230−400 mesh) by the flash technique.[27] All reactions were carried out under either argon or nitrogen in oven (150 °C)-dried or flame-dried glassware.

General Procedure for Preparation of 3-Cyano-4-benzopyrones. Preparation of *O*-Methyl Oximes. To a heterogeneous mixture of 3-formyl-4-benzopyrone (5.0−10.0 mmol) and H_2NOMe−HCl (1.25 equiv) in 20−50 mL of 95% EtOH was added 1−3 drops of concentrated HCl (∼12 N). The mixture was refluxed for 3−6 h, and in most cases, a homogeneous pale-yellow solution was obtained. The progress of the reaction could be monitored by TLC (5% Et_2O in CH_2Cl_2), but the reaction was essentially complete within 3 h. In addition, overheating did not lead to lower yield since these *O*-methyl oximes are very robust. At the end of the reaction, the mixture was concentrated to dryness under reduced pressure. The crude solid was filtered through a small pad of silica gel using 2−3% Et_2O in CH_2Cl_2 as the eluting solvent system. After the solvent was evaporated under reduced pressure and the solids were dried on a high-vacuum pump, an off-white solid was obtained and characterized as the desired *syn*/*anti* isomeric *O*-methyl oximes (yield ≥ 95% in all cases).

Preparation of 3-Cyano-4-benzopyrones. To a homogeneous solution of the *O*-methyl oxime prepared above (0.5−1.0 mmol) in anhydrous benzene (80−160 mL) was added concentrated H_2SO_4 (195.0−240.0 mg or 100.0−130.0 μL with d = ∼1.84). The reaction mixture was refluxed vigorously, and the resulting methanol byproduct was removed by using a Dean−Stark apparatus filled with anhydrous 4 Å molecular sieves. The reaction progress was monitored carefully with TLC analysis (25% or 50% EtOAc in hexane). The product has a lower R_f, whereas the starting material has a higher R_f (one spot in 25% EtOAc in hexane but two spots in 5% Et_2O in CH_2Cl_2 for both *syn* and *anti* isomers). When the starting material was mostly consumed and a decomposition (close to the baseline) occurred according to the TLC analysis, the reaction was terminated by

(26) (a) Nohara, A.; Kuriki, H.; Saijo, T.; Sugihara, H.; Kanno, M.; Sanno, Y. *J. Med. Chem.* **1977**, *20*, 0, 141. (b) Nohara, A.; Ishiguro, T.; Ukawa, K.; Sugihara, H.; Maki, Y.; Sanno, Y. *J. Med. Chem.* **1985**, *20*, 559.

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

cooling to room temperature. If necessary, ^{1}H NMR analysis was also useful to determine the extent of desired elimination and decomposition promoted by the acid. The reaction duration usually falls in the range of 8−36 h. If severe precipitation or gummy residue occurs, the final yield would likely be low. After cooling to room temperature, the mixture was first filtered through a small bed of silica gel using 25% EtOAc in hexane as the eluting solvent. The solvent was concentrated under reduced pressure, and the residue was purified by flash silica gel column chromatography[27] (gradient solvent system, 0−25% EtOAc in hexane) to provide the desired pyrones.

Characterizations of *O*-Methyl Oximes 10−18 and 30. 6-Isopropyl-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (10): R_f = 0.46 (25% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 1.29 (d, 6 H, J = 6.9 Hz), 3.03 (septet, 1 H, J = 6.9 Hz), 4.05 (s, 3 H), 7.40 (dd, 1 H, J = 2.4, 8.7 Hz), 7.57 (dd, 1 H, J = 1.8, 8.7 Hz), 7.82 (s, 1 H), 8.08 (d, 1 H, J = 2.1 Hz), 9.36 (s, 1 H); *anti* δ 1.29 (d, 6 H, J = 6.9 Hz), 3.03 (septet, 1 H, J = 6.9 Hz), 3.94 (t, 3 H, J = 0.9 Hz), 7.57 (dd, 1 H, J = 1.8, 8.7 Hz), 8.08 (d, 1 H, J = 2.1 Hz), 8.38 (d, 1 H, J = 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 33.8, 62.1, 62.8, 117.0, 118.2, 122.8, 123.0, 123.8, 133.0, 133.2, 136.9, 141.4, 146.8, 152.8, 160.2, 175.7, (missing 11 signals because of overlap); IR (neat) cm^{-1} 2962m, 1652s, 1619m; MS (EI) *m/e* (% relative intensity) 245 (7) M$^+$, 215 (19), 216 (100). Anal. Calcd for $C_{14}H_{15}NO_3$: C 68.56, H 6.16, N 5.71. Found: C 68.70, H 6.28, N 5.64.

4-Oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (11): R_f = 0.36 (25% EtOAc in hexane); mp 75−77 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 4.05 (s, 3 H), 7.40−7.49 (m, 2 H), 7.67−7.72 (m, 1 H) 7.80 (s, 1 H),8.24 (m, 1 H), 9.37 (s, 1 H); *anti* δ 3.95 (s, 3 H), 7.40−7.49 (m, 2 H), 7.67−7.72 (m, 1 H), 8.24 (m, 1 H), 8.29 (s, 1 H), 8.41 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.1, 62.9, 115.5, 117.2, 118.3, 124.0, 125.7, 126.0, 126.2, 134.0, 134.2, 136.7, 141.09, 141.13, 152.9, 155.7, 156.2, 160.2, 160.3, 175.4, (missing two signals because overlap); IR (neat) cm^{-1} 2941w, 1661s, 1622m; MS (EI) *m/e* (% relative intensity) 203 (7) M$^+$, 173 (16), 172 (100). Anal. Calcd for $C_{11}H_9NO_3$: C 65.02, H 4.46, N 6.89. Found: C 65.11, H 4.60, N 6.86.

6-Chloro-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (12): R_f = 0.43 (25% EtOAc in hexane); mp 97−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 4.05 (s, 3 H), 7.44 (dd, 1 H, J = 2.1, 9.0 Hz), 7.64 (dd, 1 H, J = 2.4, 9.9 Hz), 7.77 (s, 1 H), 8.20 (d, 1 H, J = 2.4 Hz), 9.37 (s, 1 H); *anti* δ 3.95 (s, 3 H), 7.44 (dd, 1 H, J = 2.1, 9.0 Hz), 7.63 (dd, 1 H, J = 2.4, 9.0 Hz), 8.20 (d, 1 H, J = 2.4 Hz), 8.26 (s, 1 H), 8.41 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.2, 63.0, 115.5, 117.4, 120.0, 120.1, 124.9, 125.4, 125.7, 131.8, 134.3, 134.5, 136.3, 136.2, 140.7, 152.9, 154.0, 154.5, 160.2, 160.3, 174.2 (missing one signal because overlap); IR (neat) cm^{-1} 2937w, 1651s, 1616m; MS (EI) *m/e* (% relative intensity) 237 (6) M$^+$, 208 (32), 207 (100). Anal. Calcd for $C_{11}H_8ClNO_3$: C 55.60, H 3.39, N 5.89. Found: C 55.31, H 3.60, N 5.83.

6-Methoxy-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (13): R_f = 0.33 (25% EtOAc in hexane); mp 119−121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 3.94 (d, 3 H, J = 2.7 Hz), 4.04 (s, 3 H), 7.27 (dd, 1 H, J = 3.0, 8.9 Hz), 7.41 (d, 1 H, J = 9.3 Hz), 7.60 (d, 1 H, J = 3.0 Hz), 7.82 (s, 1 H), 9.35 (s, 1 H); *anti* δ 3.90 (s, 3 H), 3.94 (d, 3 H, J = 2.7 Hz), 7.27 (dd, 1 H, J = 3.0, 9.0 Hz), 7.42 (d, 1 H, J = 9.0 Hz), 7.59 (d, 1 H, J = 3.0 Hz), 8.31 (s, 1 H), 8.40 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 62.1, 62.8, 105.1, 105.2, 105.3, 105.4, 114.8, 116.5, 119.7, 124.1, 124.7, 136.9. 137.0, 141.3, 141.4, 151.1, 152.7, 157.4, 159.9, 160.0, 175.3 (missing two signals because of overlap); IR (neat) cm^{-1} 3085w, 2940w, 1651s, 1615m; MS (EI) *m/e* (% relative intensity) 233 (12) M$^+$, 202 (100). Anal. Calcd for $C_{12}H_{11}NO_4$: C 61.80, H 4.75, N 6.01. Found: C 62.00, H 4.87, N 6.11.

6-Fluoro-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (14): R_f = 0.38 (25% EtOAc in hexane); mp 144−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 4.05 (s, 3 H), 7.38−7.53 (m, 2 H), 7.88 (dd, 1 H, J = 2.4, 8.1 Hz), 7.78 (s, 1 H), 9.39 (s, 1 H); *anti* δ 3.95 (s, 3 H), 7.38−7.53 (m, 2 H), 7.88 (dd, 1 H, J = 2.7, 8.1 Hz), 8.27 (d, 1 H, J -= 0.6 Hz), 8.42 (d, 1 H, J = 0.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.2, 63.0, 110.9 (d, J = 24.2 Hz), 111.0 (d, J = 23.6 Hz), 114.9, 116.7, 120.6, 122.4, 125.2, 136.4, 136.3, 140.8, 140.8, 153.0, 158.2, 160.4, 161.5 (d, J = 247.7 Hz), 174.7 (missing four signals because of overlap); IR (neat) cm^{-1} 2940w, 1652s; MS (EI) *m/e* (% relative intensity) 221 (7) M$^+$, 191 (16), 192 (100). Anal. Calcd for $C_{11}H_8FNO_3$: C 59.73, H 3.65, N 6.33. Found: C 59.60, H 3.75, N 6.08.

6-Chloro-7-methyl-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (15): R_f = 0.44 (25% EtOAc in hexane); mp 150−153 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 2.49 (s, 3 H), 4.05 (s, 3 H), 7.35 (s, 1 H), 7.76 (s, 1 H), 8.36 (s, 1 H), 9.32 (s, 1 H); *anti* δ 2.49 (s, 3 H), 3.95 (s, 3 H), 7.36 (s, 1 H), 8.15 (s, 1 H), 8.25 (s, 1 H), 8.36 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 62.3, 63.1, 115.5, 117.3, 120.3, 123.1, 123.2, 125.8, 126.0, 132.6, 132.7, 136.5, 141.0, 143.6, 143.9, 152.9, 154.1, 154.6, 160.3, 174.4 (missing three signals because of overlap); IR (neat) cm^{-1} 3070w, 1649s, 1620m; MS (EI) *m/e* (% relative intensity) 251 (5) M$^+$, 222 (34), 221 (19), 220 (100). Anal. Calcd for $C_{12}H_{10}ClNO_3$: C 57.27, H 4.01, N 5.57. Found: C 57.43, H 4.14, N 5.55.

6,8-Dimethyl-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (16): R_f = 0.41 (25% EtOAc in hexane); mp 103−106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 2.37 (s, 3 H), 2.40 (s, 3 H), 4.02 (s, 3 H), 7.29 (s, 1 H), 7.76 (s, 1 H), 8.38 (s, 1 H), 9.34 (s, 1 H); *anti* δ 2.37 (s, 3 H), 2.40 (s, 3 H), 3.92 (s, 3 H), 7.29 (s, 1 H) 7.79 (s, 1 H), 8.25 (s, 1 H), 8.38 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 15.5, 21.0, 62.2, 62.9, 115.2, 116.8, 123.0, 123.2, 123.7, 123.8, 127.6, 135.2, 135.3, 136.4, 136.6, 137.1, 141.6, 152.6, 153.2, 153.2, 160.0, 175.8 (missing three signals because of overlap); IR (neat) cm^{-1} 3064w, 2971w, 1650s, 1620m; MS (EI) *m/e* (% relative intensity) 231 (7) M$^+$, 201 (17), 200 (100). Anal. Calcd for $C_{13}H_{13}NO_3$: C 67.52, H 5.67, N 6.06. Found: C 67.50, H 5.78, N 5.95.

6,8-Dibromo-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (17): R_f = 0.53 (25% EtOAc in hexane); mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 4.07 (s, 3 H), 8.03 (d, 1 H, J = 2.4 Hz), 8.30 (d, 1 H, J = 2.4 Hz), 8.48 (s, 1 H), 9.46 (s, 1 H); *anti* δ 3.96 (s, 3 H), 8.03 (d, 1 H, J = 2.4 Hz), 8.22 (s, 1 H), 8.30 (d, 1 H, J = 2.4 Hz), 8.48 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.5, 63.3, 113.30, 113.33, 115.8, 117.9, 119.2, 119.3, 126.2, 126.3, 128.2, 128.5, 135.9, 140.0, 140.1, 140.3, 153.0, 160.3, 173.8 (missing three signals because of overlap); IR (neat) cm^{-1} 3070w, 2940w, 1659s, 1614w; MS (EI) *m/e* (% relative intensity) 363 (5), 361 (11), 359 (5) M$^+$, 332 (49), 331 (20), 330 (100). Anal. Calcd for $C_{11}H_7Br_2NO_3$: C 36.60, H 1.95, N 3.88. Found: C 36.73, H 1.86, N 3.88.

6,8-Dichloro-4-oxo-4*H*-1-benzopyran-3-carboxaldehyde 3-*O*-methyl oxime (18): R_f = 0.56 (25% EtOAc in hexane); mp 146−149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *syn* δ 4.05 (s, 3 H), 7.70 (d, 1 H, J = 2.4 Hz), 8.06 (d, 1 H, J = 2.4 Hz), 8.45 (s, 1 H), 9.42 (s, 1 H); *anti* δ 3.94 (s, 3 H), 7.71 (d, 1 H, J = 2.4 Hz), 8.06 (d, 1 H, J = 2.4 Hz), 8.19 (s, 1 H), 8.45 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.5, 63.2, 115.8, 117.9, 124.3, 124.8, 125.8, 125.9, 131.5, 131.6, 134.3, 134.5, 135.8, 140.3, 150.7, 152.9, 160.1, 173.8, 173.9 (missing three signals because of overlap); IR (neat) cm^{-1} 3073w, 2946w, 1665s; MS (EI) *m/e* (% relative intensity) 271 (6) M$^+$, 242 (65), 240 (100). Anal. Calcd for $C_{11}H_7Cl_2NO_3$: C 48.56, H 2.59, N 5.15. Found: C 48.35, H 2.66, N 5.02.

1-Oxo-1*H*-naphtho[2,1-*b*]pyran-2-carboxaldehyde (29). The aldehyde **29** was prepared according to literature procedures:[15b] R_f = 0.51 (5% Et_2O in CH_2Cl_2); mp 188−190 °C; lit. mp 192−194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, 1 H, J = 9.0 Hz), 7.65−7.71 (m, 1 H), 7.78−7.84 (m, 1 H), 7.95 (dd, 1 H, J = 1.3, 8.1 Hz), 8.16 (d, 1 H, J = 9.0 Hz), 8.56 (s, 1 H), 10.00 (dd, 1 H, J = 0.6, 8.6 Hz), 10.51 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.3, 118.9, 122.2, 126.9, 127.4, 128.4, 129.8, 130.3, 131.0, 136.6, 157.5, 158.1, 177.7, 189.3; IR (neat) cm^{-1} 2853w, 1697m, 1651s; MS (EI) *m/e* (% relative intensity) 224 (14) M$^+$, 196 (100). Anal. Calcd for $C_{14}H_8O_3$: C 75.00, H 3.60. Found: C 75.19, H 3.71. Chemical Abstracts Registry Number: 23469-50-3 (supplied by author).

1-Oxo-1*H*-naphtho[2,1-*b*]pyran-2-carboxaldehyde 3-*O*-methyl oxime (30). R_f = 0.62 (5% Et_2O in CH_2Cl_2); mp 102−105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ *syn* 3.95 (s, 3 H), 7.08 (d, 1 H, J = 9.0 Hz), 7.42−7.36 (m, 1 H), 7.56−7.50 (m, 1 H), 7.59 (d, 1 H, J = 8.0 Hz), 7.71 (d, 1 H, J = 8.9 Hz), 7.73 (s, 1 H), 9.00 (s, 1 H), 9.68 (d, 1 H, J = 8.6 Hz); *anti* 3.88 (s, 3 H), 7.10 (d, 1 H, J = 9.1 Hz), 7.42−7.36 (m, 1 H), 7.56−7.50 (m, 1 H), 7.59 (d, 1 H, J = 8.0 Hz), 7.71 (d, 1 H, J = 8.9 Hz), 8.10 (s, 1 H), 8.19 (s, 1 H), 9.73 (d, 1 H, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.0, 62.7, 117.1, 117.5, 119.5, 126.8, 128.3, 128.4, 129.3, 129.4, 130.3, 130.7, 135.7, 135.9, 136.8, 141.4, 150.4, 156.9, 157.5, 157.8, 176.6, 176.7 (missing eight signals because of overlap); IR (neat)

cm^{-1} 3079w, 2960w, 2932w, 1641s, 1610m; MS (EI) *m/e* (% relative intensity) 253 (6) M^+, 222 (100). Anal. Calcd for $C_{15}H_{11}NO_3$: C 71.14, H 4.38, N 5.53. Found: C 70.92, H 4.47, N 5.66.

Characterizations for 3-Cyano-4-benzopyrones 19−27 and 31. 6-Isopropyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (19): R_f = 0.24 (25% EtOAc in hexane); mp 119−120 °C; lit. mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (dd, 6 H, J = 1.2, 6.9 Hz), 3.05 (octet, 1 H, J = 6.8 Hz), 7.46 (dd, 1 H, J = 0.9, 8.4 Hz), 7.65 (ddd, 1 H, J = 0.6, 1.5, 8.8 Hz), 8.08 (d, 1 H, J = 2.1 Hz), 8.37 (d, 1 H, J = 1.2 Hz). Chemical Abstracts Registry Number: 50743-32-3 (supplied by author).

4-Oxo-4*H*-1-benzopyran-3-carbonitrile (20): R_f = 0.37 (50% EtOAc in hexane); mp 177−179 °C; lit. mp 177−178 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (t, 1 H, J = 7.2 Hz), 7.54 (d, 1 H, J = 8.4 Hz), 7.79 (m, 1 H), 8.26 (dd, 1 H, J = 1.8, 8.4 Hz), 8.40 (d, 1 H, J = 0.6 Hz). Chemical Abstracts Registry Number: 50743-17-4 (supplied by author).

6-Chloro-4-oxo-4*H*-1-benzopyran-3-carbonitrile (21): R_f = 0.35 (50% EtOAc in hexane); mp 211−213 °C; lit. mp 210−213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, 1 H, J = 9.0 Hz), 7.73 (ddd, 1 H, J = 0.6, 2.7, 8.7 Hz), 8.22 (d, 1 H, J = 2.4 Hz), 8.40 (d, 1 H, J = 0.6 Hz). Chemical Abstracts Registry Number: 50743-20-9 (supplied by author).

6-Methoxy-4-oxo-4*H*-1-benzopyran-3-carbonitrile (22): R_f = 0.24 (25% EtOAc in hexane); mp 184−186 °C; lit. mp 194−195 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 7.33 (dd, 1 H, J = 3.0, 9.0 Hz), 7.36 (d, 1 H, J = 9.0 Hz), 7.59 (d, 1 H, J = 3.0 Hz), 8.39 (s, 1 H). Chemical Abstracts Registry Number: 50743-21-0 (supplied by author).

6-Fluoro-4-oxo-4*H*-1-benzopyran-3-carbonitrile (23): R_f = 0.34 (50% EtOAc in hexane); mp 172−174 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47−7.60 (m, 2 H), 7.90 (dd, 1 H, J = 3.0, 7.7 Hz), 7.41 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.8, 102.7, 111.7, 121.1 (d, J = 8.2 Hz), 123.8 (d, J = 25.2 Hz), 125.0, 138.6, 152.2, 160.6 (d, J = 250.6 Hz), 162.3, 171.9; IR (neat) cm^{-1} 3070w, 2240w, 1660s, 1628m; MS (EI) *m/e* (% relative intensity) 189 (100) M^+, 188 (14), 161 (20). Anal. Calcd for $C_{10}H_4NO_2F$: C 63.50, H 2.13, N 7.41. Found: C 63.49, H 2.36, N 7.28.

6-Chloro-7-methyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (24): R_f = 0.43 (50% EtOAc in hexane); mp 232−235 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3 H), 7.43 (s, 1 H), 8.19 (s, 1 H), 8.36 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 101.5, 113.5, 121.7, 122.4, 124.8, 132.8, 145.0, 154.3, 166.0, 172.0; IR (neat) cm^{-1} 3066w, 2247w, 1663s, 1621m; MS (EI) *m/e* (% relative intensity) 219 (100) M^+, 218 (10), 217 (26), 170 (24), 168 (74). Anal. Calcd for $C_{11}H_6NO_2Cl$: C 60.16, H 2.75, N 6.38. Found: C 59.94, H 2.91, N 6.14.

6,8-Dimethyl-4-oxo-4*H*-1-benzopyran-3-carbonitrile (25): R_f = 0.22 (25% EtOAc in hexane); mp 182−184 °C; lit. mp 196−198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.44 (s, 3 H), 2.46 (s, 3 H), 7.43 (s, 1 H), 7.87 (s, 1 H), 8.42 (s, 1 H). Chemical Abstracts Registry Number: 50743-40-3 (supplied by author).

6,8-Dibromo-4-oxo-4*H*-1-benzopyran-3-carbonitrile (26): R_f = 0.49 (25% EtOAc in hexane); mp 191−194 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 1 H, J = 2.4 Hz), 8.32 (d, 1 H, J = 2.4 Hz), 8.51 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.6, 111.5, 113.6, 121.0, 125.6, 128.3, 141.4, 151.8, 162.3, 170.8; IR (neat) cm^{-1} 3071w, 2224w, 1660s; MS (EI) *m/e* (% relative intensity) 331 (49), 329 (100), 327 (49) M^+, 280 (43), 278 (83), 276 (43). Anal. Calcd for $C_{10}H_3NO_2Br_2$: C 36.51, H 0.92, N 4.26. Found: C 36.70, H 1.06, N 4.08.

6,8-Dichloro-4-oxo-4*H*-1-benzopyran-3-carbonitrile (27). R_f = 0.21 (10% EtOAc in hexane); mp 166−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, 1 H, J = 2.4 Hz), 8.11 (d, 1 H, J = 2.4 Hz), 8.49 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.5, 111.3, 124.3, 125.1, 125.2, 133.2, 135.5, 150.2, 161.9, 170.7; IR (neat) cm^{-1} 3074w, 2241m, 1671s; MS (EI) *m/e* (% relative intensity) 241 (50), 240 (15) M^+, 239 (75), 188 (100). Anal. Calcd for $C_{10}H_3NO_2Cl_2$: C 50.04, H 1.26, N 5.84. Found: C 49.94, H 1.16, N 5.69.

1-Oxo-1*H*-naphtho[2,1-*b*]pyran-2-carbonitrile (31): R_f = 0.40 (50% EtOAc in hexane); mp 182−184 °C, lit. mp 194.5−195.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (d, 1 H, J = 9.1 Hz), 7.68−7.73 (m, 1 H), 7.81−7.84 (m, 1 H), 7.97 (d, 1 H, J = 8.0 Hz), 8.20 (d, 9.1 Hz, 1 H), 8.46 (s, 1 H), 9.82 (dd, 0.6 Hz, 9.2 Hz, 1 H). Chemical Abstracts Registry Number: 50743-28-7 (supplied by author).

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Supporting Information Available: ^{1}H NMR spectra of *O*-methyl oximes **10**−**18** and **30** and 3-cyano-4-benzopyrones **19**−**27** and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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