Base-PromotedSelectiveSynthesisof2H-PyranonesandTetrahydronaphthalenesviaDominoReactions

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Supporting Information

ABSTRACT: A highly efficient domino protocol has been developed for the synthesis of 6-aryl-4-(methylthio/amine-1-yl)-2-oxo-2H-pyran-3-carbonitriles and 4-aryl-2-(amine-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitriles from simple and readily available α-aryleketene dithioacetals, malononitrile, secondary amines, and cyclohexanone. This elegant domino process involved consecutive addition–elimination, intramolecular cyclization, and ring opening and closing sequences. Notably, in situ generated 2-imino-4-(methylthio/amine-1-yl)-6-aryl-2H-pyran-3-carbonitrile plays multiple roles in the construction of various novel polyaromatic hydrocarbons.

INTRODUCTION

Organic fluorescent molecules are useful to meet the important challenges between organic chemistry and materials science. In common, the structural features of small organic functional fluorophores embedded within N-, O-, and S-atom-containing common, the structural features of small organic functional fluorophores are particularly used in organic light emitting diodes (OLEDs), liquid crystal displays (LCDs) of mobile phones, fluorescent dyes, and highly effective sensor and biological probes. In addition, the small polycyclic aromatic hydrocarbon fluorophores and small biconjugated linear and nonlinear aromatic molecules with built-in donor–acceptor (D–A) architectures have amazing applications in electro-luminescent (EL) materials.

α-Pyrone moieties are a significant class of six-membered oxygen heterocyclic scaffolds. They are widely found in biologically important natural alkaloids, plants, and marine sources (Figure 1). Especially, 6-aryl-4-(methylthio/amine-1-yl)-2-oxo-2H-pyran-3-carbonitriles are versatile intermediates in the synthesis of various heterocycles/carbocycles and different D–A-containing heteroaromatic or polycyclic organic fluorophores. The other 4H-pyranone and fused pyranone derivatives are also known to possess red EL properties and dye lasers. Furthermore, Komatsu et al. reported the fluorescence properties of highly substituted pyranone (3,4,6-triphenyl-2H-pyrones) and its relevant compounds. On the other hand, naphthalene-based fluorophores and their derivatives are widely applicable in the field of OLEDs. They not only have interesting optical properties but also possess pharmacologically active biological systems as an environmentally sensitive dye (Figure 1). One of the common examples of the naphthalene-based fluorophores is 6-propionyl-2-dimethylaminonaphthalene (PRODAN). Photophysical, electrochemical, and bioapplications of PRODAN derivatives have been reported. Various core structural elements of PRODAN derivatives are present in nature and in synthetic organic compounds such as thiol-reactive acrylodan and amino acid-containing aladan.

Over the past few years, significant approaches have been developed for the construction of pyranones through traditional methods or by different transition-metal-catalyzed reactions. Particularly, Tominaga et al. reported the use of methyl-2-cyano-3,3-bis(methylthio)acrylate and different substituted acetoephones to construct 2H-pyranones under basic conditions. Furthermore, Tominaga and his co-workers also demonstrated different secondary amines and 2H-pyranone for the preparation of 2-oxo-6-aryl-4-(amine-1-yl)-2H-pyran-3-carbonitriles. However, numerous known synthetic methodologies are available for preparing naphthalene and its derivatives. Recently, some pioneering approaches have been explored for the synthesis of different D–A-containing naphthalene fluorophores in the presence of palladium-catalyzed cross-coupling via a cycloaddition reaction, Friedel–Crafts bromination of 1-cyanonaphthalene. Furthermore, a palladium acetate-induced cross-coupling reaction of 1-bromo-5-cyanonaphthalene and Ram’s group disclosed an expedient route to the synthesis of 4-aryl-2-(amine-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitriles via base-promoted 2-oxo-6-aryl-4-(amine-1-yl)-2H-pyran-3-carbonitrile with cyclohexanone derivatives.

Owing to the significance of molecular diversity and photophysical properties of small organic fluorophore scaffolds, the development of new synthetic routes is a great challenge in organic chemistry. Among the various synthetic approaches, domino reactions have emerged as a powerful tool for the
construction of highly attractive heterocycles and organic materials.\textsuperscript{23} This reaction not only enables the formation of C–C−, C–H−, and C–heteroatom-containing molecules but also omits multistep synthesis, isolation, and purification of intermediates. However, the reports on the synthesis of 2\textsubscript{H}-pyranone and naphthalene derivatives from the above investigated routes are limited and suffer from certain limitations, such as the use of moisture and air-sensitive reagents, prolonged reaction times, low yields, multistep synthesis, and isolation and purification of intermediates.

Despite the advancements, there is still a demand for the construction of pyranone and naphthalene fluorophores from easily accessible intermediates through domino reactions.\textsuperscript{24} α-Oxoketene dithioacetals (OKDTAs) are one of the versatile intermediates\textsuperscript{25} and are used to construct various heterocycles\textsuperscript{25} and fluorescence-based sensor\textsuperscript{16} molecules through ring annihilations and cyclizations. On the basis of the versatility and nature of OKDTAs, over the past few years, our research group is involved in developing new and efficient synthetic methodologies for preparing novel and biologically active heterocycles, such as spiro-oxindole,\textsuperscript{27} 2-styrylbenzimidazole,\textsuperscript{28} pyrrolylpyrimidine,\textsuperscript{28} and pyrrolylpyrazole\textsuperscript{29} derivatives via the domino reaction and multicomponent operation. Recently, we have developed a new methodology for the synthesis of functionalized 2-aryl benzimidazoles\textsuperscript{30} from α-arylketene dithioacetals (AKDTAs, 1) via domino reaction. Tominaga and co-workers demonstrated the reaction between 1 and 2-phenylethynitrile for the synthesis of 4-(methylthio)-3,6-diarylpyridin-2(1\textsubscript{H})-ones in the presence of NaOH in dimethyl sulfoxide (DMSO) (Scheme 1A).\textsuperscript{31} However, we also tried to carry out the reaction between simple and readily available 1 and malononitrile (2) under KOH base in dimethylformamide.
di-and reactions with other substrates resulted in the construction of domino process integrated consecutive addition operation. In our hypothesis, this elegant yield (Scheme 1B). This interesting result further motivated us to synthesize 2H-pyranones 3 and 5 by the domino reaction operation.

To the best of our knowledge, no reports were available to generate aryl-substituted 2H-pyranones and malononitrile (1). Subsequently, the model reaction was carried out in DMF in the presence of sodamide (NaNH2) base at rt for 12 h to obtain the corresponding product 3a in 34% yield (Table 1, entry 5). Surprisingly, product 3a was afforded in excellent yield (75%) when an attempt was made using potassium hydroxide (KOH) in DMF solvent for 3 h at rt (Table 1, entry 6). To improve the selectivity and yield of the product, the reaction was performed in NaH/THF, and the desired product 3a was obtained selectively in 30% yield at rt (Table 1, entry 4).

RESULTS AND DISCUSSION

AKDTAs of 3,3-bis(methylthio)-1-aryl-prop-2-en-1-ones (1) were synthesized by following previously reported procedures. To optimize the reaction conditions, compounds 3,3-bis(methylthio)-1-phenylprop-2-en-1-one (1a) and malononitrile (2) were taken as examples (Table 1). Initially, we started screening by using catalytic amount of piperidine (1.2 mmol) under a solvent-free condition at room temperature (rt) for 12 h; however, the reaction was not successful (Table 1, entry 1). Then, ethanol was used as a solvent in the presence of catalytic amount of piperidine under reflux conditions. To our delight, we isolated two different products 4-(methylthio)-2-oxo-6-phenyl-2H-pyran-3-carbonitrile (3a) and 2-oxo-6-phenyl-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile (5a) with 15 and 20% yields, respectively (Table 1, entry 2). The above result clearly explained the elimination of methanethiol (HSMe) by an amine to furnish 5a with good yield than 3a. Consequently, a further attempt was made using piperidin in a tetrahydrofuran (THF) solvent that furnished 5a and 5b in 20 and 24% yields, respectively (Table 1, entry 3). To further improve the selectivity and yield of the product, the reaction was performed in NaH/THF, and the desired product 3a was obtained selectively in 34% yield (Table 1, entry 5). Surprisingly, product 3a was afforded in excellent yield (75%) when an attempt was made using potassium hydroxide (KOH) in DMF solvent for 3 h at rt (Table 1, entry 6). To improve the yield of product 3a, the reaction was performed in DMF using KOH base under reflux conditions at 100 °C for 2 h, which provided 3a in 88% yield (Table 1, entry 7). The yield of 3a was decreased when the reaction was conducted in DMSO at 100 °C (Table 1, entry 8).

With the optimized reaction conditions of 3a (Table 1, entry 7), the base-promoted three-component domino reaction was further explored to obtained 5a by involving 1a and 2 with various secondary amines 4. First, we evaluated that the reaction in DMF/KOH under rt for 12 h in the presence of piperidine (4a) afforded 3a and 5a in 35 and 46% yields, respectively (Table 1, entry 9). For further improvement of the yield and selectivity, the reaction proceeded in DMF/KOH in the presence of piperidine (4a) under reflux conditions; surprisingly, the reaction was completed in 3 h with 87% yield (Table 1, entry 10). Then, the reaction of 1 and 2 with pyrrolidine (4b) performed in DMF/KOH at 100 °C for 3 h

| entry | solvent | base | secondary amine (4) | conditions | time (h) | yield of 3a (%) | yields of 5a and 5b (%) |
|-------|---------|------|----------------------|------------|----------|-----------------|-----------------------|
| 1     | none    | piperidine | secondary amine (4) | rt; no reflux | 12       | Nr (4e)         | Nr (4e)               |
| 2     | EtOH    | piperidine | secondary amine (4) | 80 °C; 12 h | 12       | 15h (4f)        | 20 (5a) (4f)           |
| 3     | THF     | piperidine | secondary amine (4) | 70 °C; 12 h | 12       | 20h (4f)        | 24 (5a) (4f)           |
| 4     | THF     | NaH     | secondary amine (4) | rt; no reflux | 12       | 30h (4f)        |                       |
| 5     | DMF     | NaNH2   | secondary amine (4) | rt; no reflux | 12       | 34h (4f)        |                       |
| 6     | DMF     | KOH     | secondary amine (4) | rt; no reflux | 3        | 75 (4f)         |                       |
| 7     | DMF     | KOH     | secondary amine (4) | 100 °C; 2 h | 2        | 88 (4f)         |                       |
| 8     | DMSO    | KOH     | secondary amine (4) | 100 °C; 5 h | 5        | 70 (4f)         |                       |
| 9     | DMF     | KOH     | piperidine           | rt; no reflux | 12       | 35 (4f)         | 46 (5a)               |
| 10    | DMF     | KOH     | piperidine           | 100 °C; 3 h | 3        | 87 (5a)         |                       |
| 11    | DMF     | KOH     | pyrrolidine          | 100 °C; 3 h | 3        | 88 (5b)         |                       |
| 12    | DMSO    | KOH     | piperidine           | 100 °C; 6 h | 6        | 60 (5a)         |                       |

**Table 1. Effect of Solvent, Base, and Secondary Amines on the Synthesis of 3a**

*The reaction was conducted with 1a (0.1 mmol) and malononitrile (2, 0.1 mmol). The reaction was conducted with 1a (0.1 mmol), malononitrile (2, 0.1 mmol), and secondary amines (4, 0.2 mmol). Piperidine/pyrrolidine used: 0.2 mmol (2 equiv) for all of the reactions. Bold indicates desired product with good yield.*
afforded 88% of the desired product (Table 1, entry 11). A further final attempt made by using potassium hydroxide as a base in DMSO afforded the product in a lower yield (60%) under 100 °C at 6 h (Table 1, entry 12).

Further investigations observed that various aryl-substituted 1 adversely affect the yield (Scheme 2). The electron-rich (e.g., 3-OMe) and halogenated (e.g., 4-Br) phenyl rings were successfully converted into the final products in good yield (Scheme 2, 3b and 3c). 1-Naphthyl- and 2-naphthyl-substituted AKDTAs also provided the corresponding product in good yield (Scheme 2, 3d and 3e). All of the synthesized 3a—e and 5a—j compounds were well-characterized and confirmed by IR, 1H, 13C NMR, and mass spectroscopy. Following the current methodology, our desired products 3a and 5a were scaled up to 5 g with 85 and 82%, respectively, under optimized reaction conditions (Scheme 3).

On the basis of the previous literature reports,31,32 the plausible reaction mechanism for the formation of 3 and 5 is proposed in Scheme 4. In the presence of a base, malononitrile 2 underwent nucleophilic attack at the β-carbon of AKDTAs, followed by loss of a methythio group, which leads to the formation of intermediate B. Furthermore, intermediate B underwent intramolecular O-cyclization to form intermediate D (2-imino-4-(methylthio/amine-1-yl)-6-aryl-2H-pyran-3-carbonitrile). Finally, in the presence of acid, intermediate D underwent hydrolysis to furnish desired products 3 and 5.

On the basis of the synthetic utility and the scope of this methodology, AKDTAs (1) were further subjected to react with secondary amines, malononitrile, and cyclohexanone under reflux (100 °C) conditions in KOH/DMF via four-component domino reactions. To optimize the reaction conditions, 1a (1 mmol), piperidine (4a, 2 mmol), malononitrile (2, 1 mmol), and cyclohexanone (6, 1 mmol) were refluxed at 100 °C in the presence of KOH (2.2 mmol)/DMF to afford 7a in 87% yield (Scheme 5). Structural varieties of secondary amines (piperidine/pyrrolidine, 4) and AKDTAs (1) have been successfully utilized for this transformation (Scheme 5). The synthesized novel tetrahydronaphthalene derivatives 7a—j have been obtained in excellent yield (76—88%) with AKDTAs by in situ generation of the pyranone intermediate via the addition—elimination, cyclization, and ring opening and closing techniques. Interestingly, we have successfully synthesized highly congested binaphthyl-type products 7g,7h and 7i,7j in good yields (Figure 2) by using corresponding AKDTAs 1d, 1e under optimized reaction conditions. All of the synthesized tetrahydronaphthalenes 7a—j were confirmed with the help of IR, 1H, 13C NMR, and mass spectroscopy techniques.

On the basis of the previous literature reports,31,32 the plausible reaction mechanism was proposed for the formation of 7 in Scheme 6. The reaction was first initiated by the secondary amines (4). This 4 underwent reaction with AKDTAs to form intermediate A, which undergoes nucleophilic attack with malononitrile (2) by loss of a methythio group, leading to the formation of intermediate B. Then, intermediate B undergoes intramolecular O-cyclization to generate 2-imino-6-aryl-4-(piperidin/pyrrolidin-1-yl)-2H-pyran-3-carbonitriles (D). Further, cyclohexanone 6 reacted at the C-6 position of in situ generated D with intramolecular cyclization involving the carbonyl group of cyclohexanone (6) to give intermediate E. Intermediate E further converted into a six-membered ring F, with ring opening followed by the elimination of isocyanic acid. Subsequently, intermediate F further underwent acidification followed by dehydration to furnish tetrahydronaphthalene 7 in excellent yields.

**CONCLUSIONS**

We have developed a novel methodology for the synthesis of 6-aryl-4-(methylthio/amine-1-yl)-2-oxo-2H-pyran-3-carbonitrile and 4-aryl-2-(amine-1-yl)-5,6,7,8-tetrahydronaphthalene-1-carbonitriles.
bonitrile derivatives with excellent yields from AKDTAs via base-catalyzed domino reactions. This methodology is simple, convenient, and highly selective for the synthesis of a D–A fluorophore without using any organometallic catalyst or reagent. The photophysical studies of the synthesized pyranone and tetrahydronaphthalene derivatives are under progress.

Scheme 3. Synthesis of 2-Oxo-6-aryl-4-(amine-1-yl)-2H-pyran-3-carbonitriles 5a–j

The reaction was performed with 1 (1 mmol), 2 (1 mmol), 4 (2 mmol), KOH (1.2 mmol), and the solvent (10 mL) under 100 °C. Isolated yields.

Scheme 4. Plausible Reaction Mechanism for the Formation of 3 and 5
EXPERIMENTAL SECTION

General Remarks. Melting points of all of the synthesized compounds were determined in open capillary tubes, and they were uncorrected. Infrared spectra were recorded on a Jasco FT-IR instrument in KBr pellets and reported in cm\(^{-1}\).

Electrospray ionization mass spectrometry (ESI-MS) were performed with an Agilent mass spectrometer and recorded in positive and negative modes. The \(^1\)H and \(^13\)C NMR spectra of the new compounds were recorded at 300 and 75 MHz in CDCl\(_3\), DMSO-\(d_6\), and trifluoroacetic acid with tetramethylsilane as the internal standard. Chemical shifts are expressed in parts per million, coupling constants (\(J\) values) are given in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), and m (multiplet). ESI-high-resolution mass spectrometry (HRMS) data were recorded with Micromass Q-TOF mass spectrometer. Thin-layer chromatography (TLC) analysis was checked by using Silica gel-G plates (Merck) a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. All chemicals were purchased from Sigma-Aldrich and used without further purification.

General Procedure for the Synthesis of 4-(Methylthio)-2-oxo-6-aryl-2\(^H\)-pyran-3-carbonitrile (3a–e).

The reaction was performed with 1 (1 mmol), 2 (1 mmol), 4 (2 mmol), 6 (1 mmol), KOH (2.2 mmol), and the solvent (10 mL) under 100 °C. 

Isolated yields.
Characterization Data. 4-(Methylthio)-2-oxo-6-phenyl-2H-pyran-3-carbonitrile (3a). Yield: 465 mg, 88%. Yellow needles, mp 200–201 °C (Lit:18 mp: 201 °C). FT-IR (KBr, cm⁻¹): 2213 (CN) and 1715 (C=O). ¹H NMR (300 MHz, CDCl₃): δ 2.74 (s, 3H, SMe), 6.73 (s, 1H, pyranone), 7.52–7.59 (m, 3H, ArH), 7.87–7.89 (m, 2H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ 14.8, 88.8, 108.6, 112.4, 116.2, 126.2, 126.9, 128.7, 129.6, 161.2, 162.8, 173.8. ESI-MS calcd m/z: 243.04; found 266.03 [M + Na]⁺.

6-(3-Methoxyphenyl)-4-(methylthio)-2-oxo-2H-pyran-3-carbonitrile (3b). Yield: 460 mg, 85%. Yellow needles, mp 180–182 °C (Lit:7b mp: 181 °C). FT-IR (KBr, cm⁻¹): 2213 (CN) and 1711 (C=O). ¹H NMR (300 MHz, DMSO-d₆): δ 2.82 (s, 3H, SMe), 3.89 (s, 3H, OMe), 7.08 (s, 1H, pyranone), 7.42–7.49 (m, 2H, ArH), 7.56–7.59 (m, 1H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ 14.8, 55.7, 88.8, 112.4, 112.5, 116.3, 119.5, 119.6, 130.0, 161.0, 162.5, 174.0. ESI-MS calcd m/z: 273.05; found 296.08 [M + Na]⁺.

6-(4-Bromophenyl)-4-(methylthio)-2-oxo-2H-pyran-3-carbonitrile (3c). Yield: 451 mg, 83%. Yellow needles, mp 230–231 °C (Lit:7b mp: 230 °C). FT-IR (KBr, cm⁻¹): 2213 (CN) and 1711 (C=O). ¹H NMR (300 MHz, DMSO-d₆): δ 3.02 (s, 3H, SMe), 6.70 (s, 1H, pyranone), 7.565–7.66 (m, 2H, ArH), 7.73 (s, 1H, ArH), 7.76–7.77 (m, 1H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ 14.9, 89.5, 112.4, 116.1, 125.7, 127.0, 127.7, 128.1, 128.9, 132.9, 161.6, 161.7, 173.4. ESI-MS calcd m/z: 320.95; found 343.98 [M + Na]⁺.

4-(Methylthio)-6-(naphthalen-1-yl)-2-oxo-2H-pyran-3-carbonitrile (3d). Yield: 415 mg, 80%. Yellow needles, mp 222–223 °C (Lit:7b mp: 222 °C). FT-IR (KBr, cm⁻¹): 2210 (CN) and 1707 (C=O). ¹H NMR (300 MHz, CDCl₃): δ 2.68 (s, 3H, SMe), 6.64 (s, 1H, pyranone), 7.54–7.64 (m, 2H, ArH), 7.75 (d, 1H, J = 9.0 Hz, ArH), 7.96 (dd, 1H, J = 9.0 Hz, ArH), 8.05 (d, 1H, J = 8.0 Hz, ArH), 8.15 (dd, 1H, J = 8.4 Hz, ArH). ¹³C NMR (75 MHz, CDCl₃): δ 14.8, 90.0, 112.6, 116.4, 123.4, 127.0, 127.0, 127.7, 128.3, 128.9, 129.0, 129.1, 129.7, 133.4, 161.2, 164.3, 172.8. ESI-MS calcd m/z: 293.05; found 316.06 [M + Na]⁺.

4-(Methylthio)-6-(naphthalen-2-yl)-2-oxo-2H-pyran-3-carbonitrile (3e). Yield: 435 mg, 84%. Yellow needles, mp 244–245 °C (Lit:7b mp: 245 °C). FT-IR (KBr, cm⁻¹): 2214 (CN) and 1713 (C=O). ¹H NMR (300 MHz, DMSO-d₆): δ 2.84 (s, 3H, SMe), 7.09 (s, 1H, pyranone), 7.53–7.59 (m, 1H, ArH), 7.91–8.02 (m, 4H, ArH). ¹³C NMR (75 MHz, CDCl₃): δ 14.8, 88.6, 112.5, 121.6, 125.6, 127.9, 127.9, 129.4, 129.6, 129.9, 132.8, 161.1, 162.4, 173.5. ESI-MS calcd m/z: 293.05; found 316.04 [M + Na]⁺.

General Procedure for the Synthesis of 2-Oxo-6-aryl-4-(piperidin/pyrrolidin-1-yl)-2H-pyran-3-carbonitrile (5a–j). A round-bottom flask was charged with 3,3-bis(methylthio)-1-aryllprop-2-en-1-one (1, 1 mmol), piperidien/pyrrolidine (4, 2 mmol), 5 mL of DMF, and powdered KOH (1.2 mmole), and the reaction mixture was set at 100 °C over a preheated oil bath for complete elimination of methylthiol. The reaction mixture was stirred for 1 h until the formation of N,S-
acetal (monitored by TLC), followed by addition of malononitrile (2, 1 mmol). The reaction mixture was further stirred for a stipulated period of time (Scheme 3). Subsequently, HCl solution (1 mL, 1 N) was added and the reaction mixture was continuously stirred for 30 min at the same temperature until the reaction was completed. Completion of the reaction was monitored by TLC. After completion of the reaction, as shown by TLC, the reaction mixture was poured onto ice water and further stirred at rt for an appropriate time. The white/pale yellow precipitates that appeared were collected by filtration. This product was washed with water and recrystallized from methanol to afford a pure white/pale yellow solid of 2-oxo-6-aryl-4-(piperidin/pyrrolidin-1-yl)-2H-pyran-3-carbonitrile (5a–j).

**Characterization Data.** 2-Oxo-6-phenyl-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile (5a). Yield: 532 mg, 87%. White solid, mp 210–211 °C (Lit2 mp: 211 °C). FT-IR (KBr, cm−1): 2209 (CN) and 1583 (C==O). 1H NMR (300 MHz, CDCl3): δ 1.81 (br, 6H, piperidine), 3.24 (br, 4H, piperidine), 6.47 (s, 1H, pyranone), 7.45–7.52 (m, 3H, ArH), 7.79–7.83 (m, 2H, ArH). 13C NMR (75 MHz, CDCl3): δ 23.7, 26.2, 50.7, 71.9, 94.6, 117.3, 126.0, 128.8, 130.5, 131.6, 160.3, 160.2. ESI-MS calcd m/z: 288.12; found 303.14 [M + Na]+.

2-Oxo-6-phenyl-4-(piperidin-1-yl)-2H-pyran-3-carbonitrile (5b). Yield: 511 mg, 88%. White solid, mp 287–288 °C (Lit2 mp: 287 °C). FT-IR (KBr, cm−1): 2210 (CN) and 1582 (C==O). 1H NMR (300 MHz, CDCl3): δ 2.14 (brs, 4H, piperidine), 3.77 (br, 2H, pyrrolidine), 4.05 (br, 2H, pyrrolidine), 6.56 (s, 1H, pyranone), 7.45–7.56 (m, 3H, ArH), 7.74–7.77 (m, 2H, ArH). 13C NMR (75 MHz, CDCl3): δ 24.2, 25.7, 51.1, 51.6, 69.5, 95.4, 112.6, 120.2, 126.0, 126.2, 129.1, 129.2, 129.6, 132.8, 160.3, 160.9, 167.1. ESI-MS calcd m/z: 266.11; found 267.09 [M + 1]+.

6-(5-Methoxyphenyl)-2-oxo-4-(pyrrolidin-1-yl)-2H-pyran-3-carbonitrile (5d). Yield: 533 mg, 86%. White solid, mp 258–260 °C. FT-IR (KBr, cm−1): 2211 (CN) and 1579 (C==O). 1H NMR (300 MHz, CDCl3): δ 1.80 (br, 6H, piperidine), 3.83–3.86 (m, 7H, [piperidine 4H and −OMe 3H are merged]), 6.45 (s, 1H, pyranone), 7.02–7.06 (m, 1H, ArH), 7.32–7.38 (m, 3H, ArH). 13C NMR (75 MHz, CDCl3): δ 23.4, 26.2, 51.4, 55.5, 95.5, 111.7, 112.6, 116.4, 118.4, 118.7, 125.7, 130.4, 130.8, 159.9, 160.4, 161.1. HRMS [M + H]+ calcd for C17H16N2O3: 296.0842; found 296.0839.

6-(5-Bromo-1H-inden-1-yl)-2-oxo-4-(pyrrolidin-1-yl)-2H-pyran-3-carbonitrile (5e). Yield: 504 mg, 85%. White solid, mp 258–260 °C. FT-IR (KBr, cm−1): 2211 (CN) and 1582 (C==O). 1H NMR (300 MHz, CDCl3): δ 2.08 (br, 4H, pyrrolidine), 3.69 (br, 2H, piperidine), 3.85 (s, 3H, −OMe), 4.10 (m, 2H, piperidine), 6.33 (s, 1H, pyranone), 7.28–7.29 (m, 1H, ArH), 7.28–7.35 (m, 3H, ArH). 13C NMR (75 MHz, CDCl3): δ 24.4, 25.7, 50.5, 50.9, 55.4, 70.3, 94.7, 112.2, 117.4, 118.0, 118.3, 129.8, 131.7, 157.0, 159.8, 162.3. HRMS [M + H]+ calcd for C17H13BrN2O3: 310.8394; found 310.8389.

6-(4-Bromophenyl)-2-oxo-4-(pyrrolidin-1-yl)-2H-pyran-3-carbonitrile (5f). Yield: 519 mg, 85%. Pale yellow solid, mp 247–248 °C (Lit5 mp: 248 °C). FT-IR (KBr, cm−1): 2211 (CN) and 1547 (C==O). 1H NMR (300 MHz, CDCl3): δ 1.81 (br, 6H, piperidine), 3.04 (br, 4H, piperidine), 6.47 (s, 1H, pyranone), 7.58–7.61 (m, 2H, ArH), 7.66–7.69 (m, 2H, ArH). 13C NMR (75 MHz, CDCl3): δ 23.4, 26.2, 51.4, 95.4, 116.4, 125.4, 126.3, 127.5, 128.3, 132.5, 160.2, 160.8, 162.6. ESI-MS calcd m/z: 358.03; found 381.02 [M + Na]+.

6-(4-Bromophenyl)-2-oxo-4-(pyrrolidin-1-yl)-5,6,7,8-tetrahydropyridine-1-carbonitrile (7a–j). The solution of 3,3-bis(methylthio)-1-arylprop-2-en-1-one (1 mmol), piperidien/ pyrrolidine (2 mmol), 5 mL of DMF, and (22 mmol) powdered KOH was stirred for 1 h at 100 °C. Afterward malononitrile (2 mmol) and cyclohexanone (6 mmol) were washed with water and recrystallized from methanol to afford a pure white/pale yellow solid of 2-oxo-6-aryl-4-(piperidin/pyrrolidin-1-yl)-2H-pyran-3-carbonitrile (5a–j).
added and the reaction mixture was further stirred for a stipulated period of time (Scheme 5). The progress of the reaction was monitored by TLC. On completion, the solvent was evaporated and the reaction mixture was poured onto crushed ice with vigorous stirring and finally neutralized with 10% HCl. The precipitate obtained was filtered and purified on a silica gel column using 10% ethyl acetate in petroleum ether as the eluent to afford a white solid of 4-aryl-2-(pyrrolidin-1-yl)-5,6,7,8-tetrahydro-1-carboximino-1-carbonitrile 7a–j.

**Characterization Data.** 4-Phenyl-2-(pyrrolidin-1-yl)-5,6,7,8-tetrahydro-1-carboximino-1-carbonitrile (7a). Yield: 604 mg, 87%. White solid, mp 107–110 °C (Lit22a mp: 108 °C). FT-IR (KBr, cm⁻¹): 670, 773, 824, 962, 1025, 1132, 1378, 1583, 2209, 2808, 2933. ¹H NMR (300 MHz, CDCl₃): δ 1.57–1.59 (m, 2H), 1.65–1.68 (m, 2H), 1.75–1.83 (m, 6H), 2.46–2.50 (m, 2H), 2.97–3.02 (m, 2H), 3.08–3.12 (m, 4H), 6.71 (s, 1H), 7.24–7.26 (m, 2H), 7.37–7.45 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 22.3, 22.8, 24.1, 26.2, 27.6, 29.0, 53.4, 105.9, 117.1, 117.8, 127.3, 128.1, 128.6, 128.8, 141.0, 142.3, 147.0, 155.1. HRMS [M + Na⁺] calc for C₂₃H₂₁N₃Na 339.1834; found 339.1834.

4-Phenyl-2-(pyrrolidin-1-yl)-5,6,7,8-tetrahydro-1-carboximino-1-carbonitrile (7b). Yield: 580 mg, 88%. White solid, mp 132–134 °C (Lit22a mp: 132 °C). FT-IR (KBr, cm⁻¹): 678, 782, 828, 967, 1029, 1137, 1380, 1588, 2208, 2810, 2934. ¹H NMR (300 MHz, CDCl₃): δ 1.62–1.66 (m, 2H), 1.79–1.83 (m, 2H), 1.94–1.98 (m, 2H), 2.37–2.42 (m, 2H), 2.93–2.97 (m, 2H), 3.55–3.59 (m, 4H), 6.41 (s, 1H), 7.25–7.27 (m, 2H), 7.35–7.40 (m, 3H). ¹³C NMR (75 MHz, CDCl₃): δ 22.6, 22.9, 25.7, 27.5, 29.3, 50.2, 95.1, 113.4, 117.5, 119.8, 123.6, 127.2, 128.0, 128.2, 139.1, 140.2, 142.5, 145.8, 149.3. HRMS [M + Na⁺] calc for C₁₀H₁₄N₂Na 225.0786; found 225.0786.

Yield: 535 mg, 84%. White solid, mp 150–152 °C. FT-IR (KBr, cm⁻¹): 760, 858, 1011, 1119, 1279, 1388, 1454, 1549, 2218, 2857, 2935. ¹H NMR (300 MHz, CDCl₃): δ 1.63–1.68 (m, 2H), 1.77–1.85 (m, 2H), 1.95–1.99 (m, 4H), 2.35–2.39 (m, 2H), 2.92–2.97 (m, 2H), 3.55–3.59 (m, 4H), 6.35 (s, 1H), 7.12–7.15 (d, J = 2H), 7.52–7.55 (d, J = 3H). ¹³C NMR (75 MHz, CDCl₃): δ 22.3, 22.7, 24.0, 26.1, 27.7, 29.0, 53.4, 106.2, 117.3, 117.5, 121.5, 121.6, 128.5, 130.3, 131.1, 139.9, 142.5, 145.7, 155.2. HRMS [M + Na⁺] calc for C₁₆H₁₀BrN₂Na 417.0942; found 419.0963.

4-(Bromophenyl)-2-(pyrrolidin-1-yl)-5,6,7,8-tetrahydro-1-carboximino-1-carbonitrile (7f). Yield: 535 mg, 84%. White solid, mp 150–152 °C. FT-IR (KBr, cm⁻¹): 760, 858, 1011, 1119, 1279, 1388, 1454, 1549, 2218, 2857, 2935. ¹H NMR (300 MHz, CDCl₃): δ 1.63–1.68 (m, 2H), 1.77–1.85 (m, 2H), 1.95–1.99 (m, 4H), 2.35–2.39 (m, 2H), 2.92–2.97 (m, 2H), 3.55–3.59 (m, 4H), 6.35 (s, 1H), 7.12–7.15 (d, J = 2H), 7.52–7.55 (d, J = 3H). ¹³C NMR (75 MHz, CDCl₃): δ 22.3, 22.7, 24.0, 26.1, 27.7, 29.0, 53.4, 106.2, 117.3, 117.5, 121.5, 121.6, 128.5, 130.3, 131.1, 139.9, 142.5, 145.7, 155.2. HRMS [M + Na⁺] calc for C₁₆H₁₀BrN₂Na 417.0942; found 419.0963.
Experimental details and spectral data for all new compounds (\(^1\)H and \(^{13}\)C NMR) (PDF)

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Notes
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