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Article

Oxidative Cyclization of 4-(2-Aminophenyl)-4-oxo-2-phenylbutanenitriles into 2-(3-Oxoindolin-2-ylidene)acetonitriles

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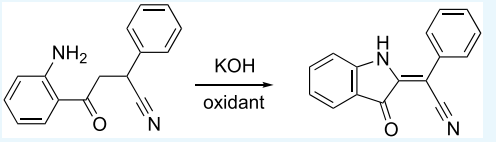
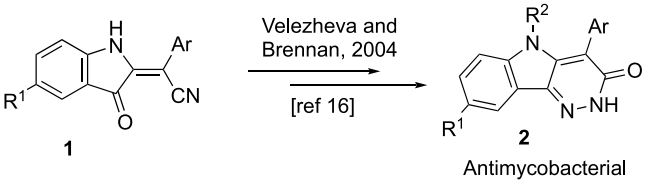
ABSTRACT: A facile and highly efficient method for the preparation of 2-(3-oxoindolin-2-ylidene)acetonitriles from 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitriles is described. The featured transformation operates via nucleophilic intramolecular cyclization and involves oxidation of the aniline moiety. Overall, this modification allowed for the improvement of yields and expansion of the reaction scope.



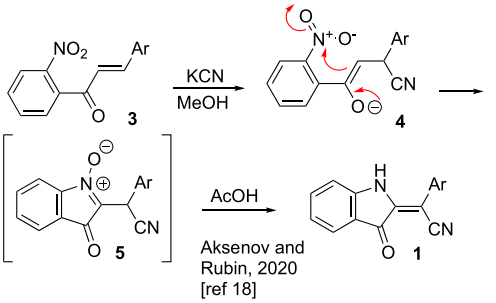
INTRODUCTION

2-Alkylideneindolin-3-one natural products and their synthetic derivatives are important synthons actively used in drug discovery and development. This heterocyclic motif possesses numerous important biological activities. Bis-indole indirubin, the main component of "Tyrian purple" dye, is a known active ingredient of a traditional Chinese herbal medicine.[1] Synthetic analogues of this dye displayed a highly selective pharmacological profile in glycogen synthase kinase and cyclin-dependent kinase inhibition.[2−7] Moreover, alkylideneindolinones were shown to induce apoptosis of human cancer cells. They are also being explored as prospective therapeutics for the treatment of several neurodegenerative conditions.[2−7] 2-Alkylideneindolin-3-one derivatives bearing a single indoline moiety or two remotely positioned indoline subunits are found in nature and are endowed with important biological activities as well.[8−15] 2-Alkylideneindolin-3-ones bearing a conjugated nitrile function (i.e., 2-(3-oxoindolin-2-ylidene)acetonitriles **1**) were used as advanced precursors in the synthesis of pyridazino[4,3-*b*]indoles **2**, which possess strong inhibitory activity against *Mycobacterium tuberculosis* (Scheme 1).[16] Recently, we have communicated on the unexpected formation of 2-alkylideneindolin-3-ones taking place upon treatment of *ortho*-nitrochalcones with potassium cyanide and acetic acid in methanol.[17] It was shown that conjugate addition of KCN to chalcone **3** triggers intramolecular attack of nucleophilic enole moiety in **4**, leading to the formation of intermediate cyclic nitronate **5** (Scheme 2). Upon addition of AcOH, the emerald-green compound could be reduced into an orange-red conjugated nitrile **1** (Scheme 2).[17] However, this attractive and simple method had serious limitations, permitting access only to indolines with non-substituted nitrogen atoms. Herein, we report on the development of a more general and efficient synthetic method to address these issues. This method takes advantage of a one-pot oxidative cyclization of *ortho*-amino-chalcones **6**, combined with optional in situ alkylation of the aniline moiety. Such an approach provides expeditious access to both 2-(3-oxoindolin-2-ylidene)acetonitriles **1** and their *N*-alkylated derivatives **7** (Scheme 3).

Scheme 1. 2-(3-Oxoindolin-2-ylidene)acetonitriles 1 as Precursors in the Preparation of Antimycobacterial Drugs



Scheme 2. Synthesis of 2-(3-Oxoindolin-2-ylidene)acetonitriles 1 via the Reductive Cyclization of Nitrochanchones 3



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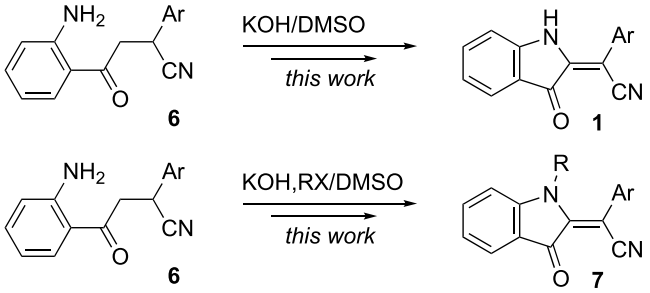
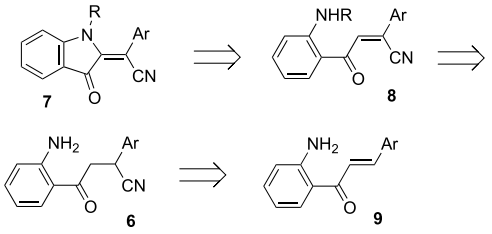
Scheme 3. Featured Method for the Preparation of 2-(3-Oxoindolin-2-ylidene)acetonitriles 1



RESULTS AND DISCUSSION

The indoline nitrogen in acetonitrile **1** is originated from the nitro group when obtained via the original method.[17] Since this involves reduction of the N−O bond in cyclic nitronate **5**, it is hardly possible to derivatize it directly into anything but an N−H bond, especially under acidic conditions. Therefore, installation of other substituents at this position to access derivatives **7** would involve additional steps in the synthetic sequence. We envisioned an alternative approach to *N*-alkylated products **7** that would involve a base-assisted 5-exo-trig conjugate addition of aniline functionality in 4-oxobut-2-enenitrile **8** (Scheme 4). The latter would be obtained by the

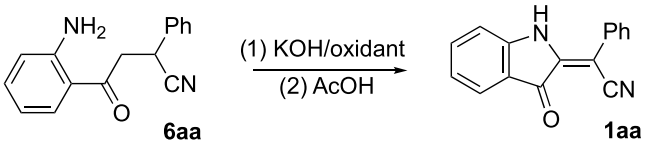
Scheme 4. Retrosynthetic Analysis of the Featured Method



oxidation of precursor **6**, which potentially could be combined with base-assisted alkylation of the primary aniline function (Scheme 4). Compound **6** should be routinely available via hydrocyanation of *ortho*-aminochalcones **9**, as described in our recent report.[18]

With this idea in mind, we attempted the oxidative cyclization of 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitrile **6aa** into **1aa** in the presence of KOH (2 equiv). The first test reaction was performed in the absence of any oxidant (in argon atmosphere). Expectedly, this led to no conversion of product, and the starting material was recovered unchanged (Table 1, entry 1). Next, the same transformation was carried in acetonitrile in the presence of strong oxidants, such as potassium permanganate or DDQ. These reactions resulted in decomposition of the starting material to form heavy tars (entries 2 and 3). Evidently, the employment of strong oxidants proved to be detrimental; therefore, we decided to test milder ones. Test reactions involving oxidation with urea complex and hydrogen peroxide in acetonitrile rendered good results (entry 4). Also, oxidation with activated carbon under oxygen atmosphere[19] looked very promising (entry 5). In contrast, oxidation with (bis(trifluoroacetoxy)iodo)benzene led to the decomposition of the starting materials without formation of the target product (entry 6). Cu(II) and SeO_2 proved inefficient as oxidants, as the reactions provided marginal yields or did not proceed at all (entries 7−9) We

Table 1. Optimization of Reaction Condition toward the Formation of 2-(3-Oxoindolin-2-ylidene)acetonitrile 1aa

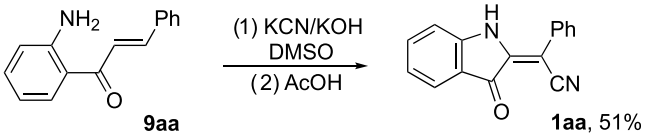


	solvent	oxidant	time, min	yield %[a]
1	DMF	none	40	NR
2	MeCN	$KMnO_4$	5	Dec.
3	MeCN	DDQ	5	Dec.
4	MeCN	H_2O_2/urea	300	60
5	DMF	O_2/C	180	64
6	MeCN	$PhI(TFA)_2$	10	Dec.
7	MeCN	$CuSO_4$	300	NR
8	MeCN	$Cu(OAc)_2$	720	15
9	MeCN	SeO_2	300	NR
10	DMF	DMSO	180	67
11	water	DMSO	120	65
12	DMSO	DMSO	40	80
13	DMSO	DMSO	60	52[b]
14	MeCN	Ph_2SO	300	65

[a]All of the test reactions were performed in 0.5 mmol scale in 5 mL vials under argon atmosphere at r.t. KOH (4 equiv) was used as a base unless specified otherwise. Quenching with AcOH (200 mg for 30 min at RT) was performed in one-pot fashion. NMR yields are provided. [b]NaOH was used instead of KOH.

also tested oxidations with dimethyl sulfoxide (DMSO) in *N*,*N*-dimethylformamide (DMF) (entry 10) or water (entry 11), which both provided good yields of **1aa**. The best results, however, were obtained when oxidation with DMSO was performed without any diluents. The reaction under these conditions was complete in 40 min, affording an 80% yield of **1aa** (entry 12). In the presence of NaOH as a base, the reaction was less efficient affording only 52% yield of the target material (entry 13). Finally, oxidation with diphenylsulfoxide in acetonitrile also occurred, although it proceeded sluggishly and provided lower yields (entry 14). It should be mentioned that this transformation may be combined with the hydrocyanation of *ortho*-aminochalcone **9aa**. Treatment with potassium cyanide and potassium hydroxide-assisted cyclization can be performed as a two-step cascade process, and the final quenching with acetic acid generates **1aa** in moderate yields (Scheme 5). While substantiating the principal

Scheme 5. Direct Synthesis of 2-(3-Oxoindolin-2-ylidene)acetonitrile 1aa from *ortho*-Aminochalcone 9aa



possibility to perform these two steps in a one-pot fashion, it proved more convenient and practical to do the sequence stepwise, as this conventional approach provides better overall yields and simplifies the purification of the final product.

With the optimized conditions in hand, we performed these transformations in a preparative scale (up to 2.00 mmol) and managed to obtain comparably high isolated yields of **1aa** (77%) (Scheme 6). The reaction demonstrated good tolerance

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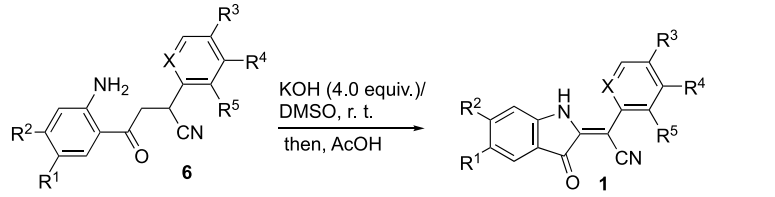
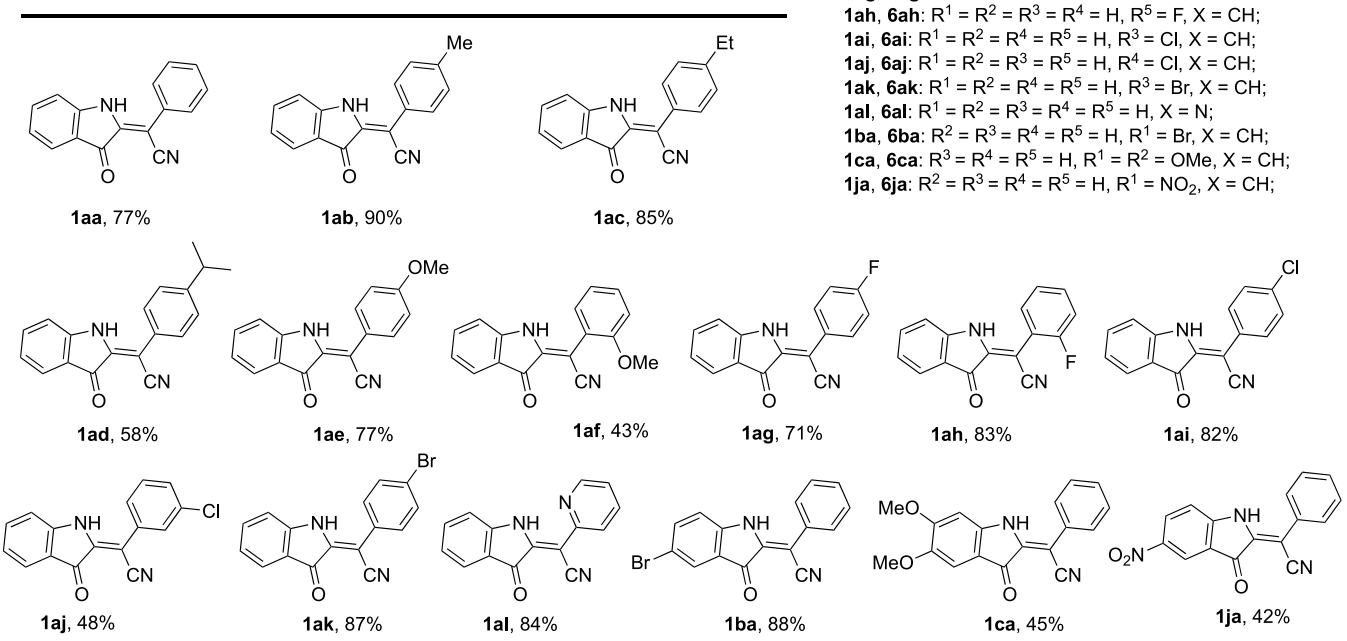
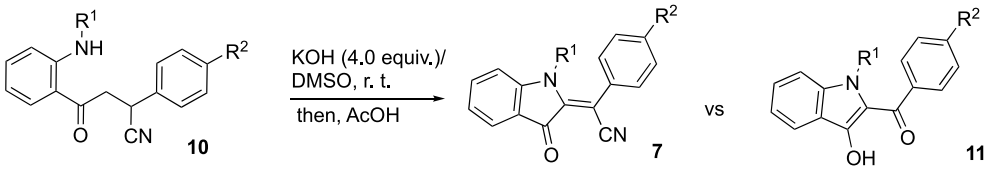
Scheme 6. Preparation of 2-(3-Oxoindolin-2-ylidene)acetonitriles 1 from 4-(2-Aminophenyl)-4-oxo-2-phenylbutanenitriles 6



1aa, **6aa**: $R^1 = R^2 = R^3 = R^4 = R^5$ = H, X = CH;
1ab, **6ab**: $R^1 = R^2 = R^4 = R^5$ = H, R^3 = Me, X = CH;
1ac, **6ac**: $R^1 = R^2 = R^4 = R^5$ = H, R^3 = Et, X = CH;
1ad, **6ad**: $R^1 = R^2 = R^4 = R^5$ = H, R^3 = *i*-Pr, X = CH;
1ae, **6ae**: $R^1 = R^2 = R^4 = R^5$ = H, R^3 = OMe, X = CH;
1af, **6af**: $R^1 = R^2 = R^3 = R^4$ = H, R^5 = OMe, X = CH;
1ag, **6ag**: $R^1 = R^2 = R^4 = R^5$ = H, R^3 = F, X = CH;
1ah, **6ah**: $R^1 = R^2 = R^3 = R^4$ = H, R^5 = F, X = CH;
1ai, **6ai**: $R^1 = R^2 = R^4 = R^5$ = H, R^3 = Cl, X = CH;
1aj, **6aj**: $R^1 = R^2 = R^3 = R^5$ = H, R^4 = Cl, X = CH;
1ak, **6ak**: $R^1 = R^2 = R^4 = R^5$ = H, R^3 = Br, X = CH;
1al, **6al**: $R^1 = R^2 = R^3 = R^4 = R^5$ = H, X = N;
1ba, **6ba**: $R^2 = R^3 = R^4 = R^5$ = H, R^1 = Br, X = CH;
1ca, **6ca**: $R^3 = R^4 = R^5$ = H, $R^1 = R^2$ = OMe, X = CH;
1ja, **6ja**: $R^2 = R^3 = R^4 = R^5$ = H, $R^1 = NO_2$, X = CH;



Scheme 7. Reactivity of 4-(2-Aminophenyl)-4-oxo-2-phenylbutanenitriles 8 with Protected Aniline Moiety

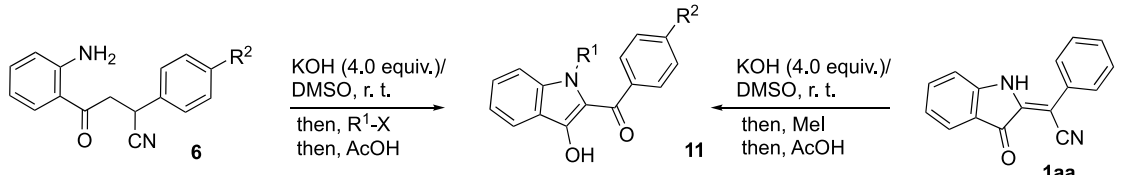


10da: R^1 = Me, R^2 = H;
10de: R^1 = Me, R^2 = OMe;
10ea: R^1 = Bn, R^2 = H;
10fa: R^1 = Ts, R^2 = H;
10ga: R^1 = Ac, R^2 = H.

7da: R^1 = Me, R^2 = H (15% from **10da**)

1aa: $R^1 = R^2$ = H (64% from **10fa**, 67% from **10ga**);

11da: R^1 = Me, R^2 = H (61% from **10da**);
11de: R^1 = Me, R^2 = OMe (77% from **10de**);
11ea: R^1 = Bn, R^2 = H (48% from **10ea**);



6aa: R^2 = H;
6ae: R^2 = OMe

11da: R^1 = Me, R^2 = H, 56%;
11de: R^1 = Me, R^2 = OMe, 72%;
11ea: R^1 = Bn, R^2 = H, 47%;

and compatibility with a variety of substituents, including methoxyarenes (**1ae**, **1af**, **1ca**), halogenated arenes (**1ag**, **1ah**, **1ai**, **1aj**, **1ak**, **1ba**), and hetarenes (**1al**) (Scheme 6).

Next, we explored the possibility to apply this approach for the preparation of *N*-substituted indole derivatives **7**. Initial attempts involved reactions of *N*-substituted precursors **10**.

Unexpectedly, these reactions took a different route entailing hydrolytic cleavage of the cyano group. Thus, upon treatment with KOH in DMSO under standard reaction conditions, *N*-methylated derivatives **10da** and **10de** supplied 2-aryloyl-3-hydroxyindoles in yields of 61 and 77%, respectively. "Normal" product **7da** was obtained in low yields with the reaction of compound **10da** only, while analogous product **7de** was not detected at all (Scheme 7). *N*-Benzylated precursor **10ea** reacted in a similar manner affording ketone **11ea** as the sole isolable product, albeit in moderate yields (Scheme 7). It also

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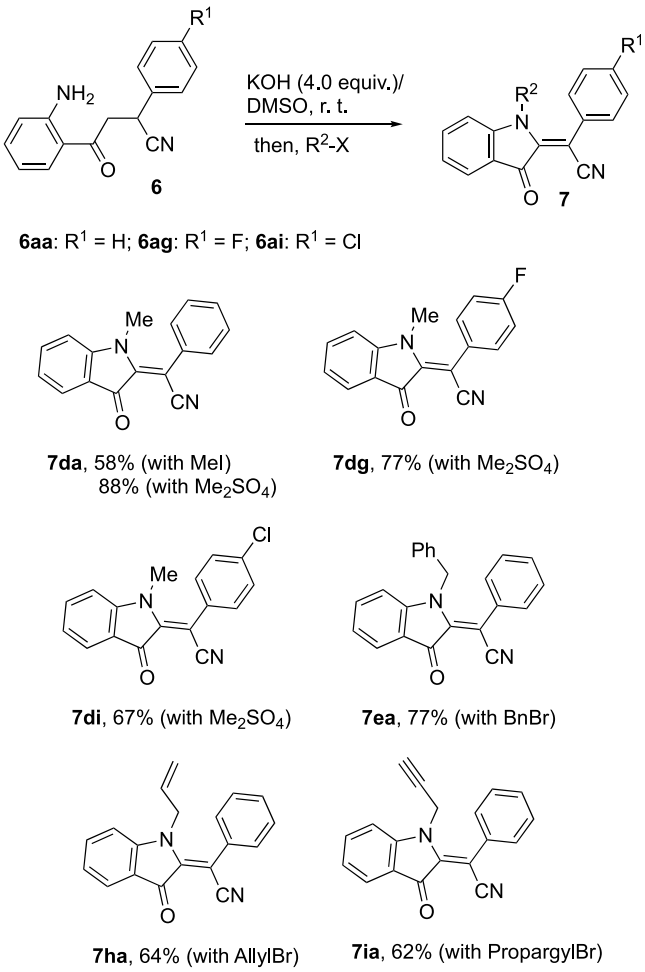
should be pointed out that we failed to engage *N*-tosylated (**10fa**) and *N*-acylated (**10ga**) 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitriles into reactions involving the formation of *N*-protected indolinone products **7**. Instead, base-assisted deprotection of the aniline moiety occurred, after which the reaction took the normal course, affording in both cases sole product **1aa** in good yields (Scheme 7). This process could be combined with the in situ alkylation of the primary amino group in 4-oxo-butanenitriles **6** with methyl iodide or benzyl bromide in DMSO in the presence of excess KOH followed by quenching with acetic acid. The corresponding 2-acylindoles **11** were formed in this case as sole products in moderate yields (Scheme 7). The same reaction could be performed employing isolated **1aa** as a starting material, which upon methylation with MeI afforded ketone **11da** in 58% yield. This suggests that **1aa** could be an intermediate in the transformation of **6aa** into **11da**.

It seems impossible to access products **7** via direct oxidative cyclization of *N*-substituted precursors **8** due to detrimental side processes, but in situ alkylation works. Accordingly, we decided to invest in a design of synthetic approach involving the featured oxidative cyclization **6** → **1** and subsequent alkylation of the indoline moiety **1** → **7**. To validate this approach, 4-(2-aminophenyl)-2-phenyl-4-oxobutyronitrile (**6aa**) was treated with KOH in DMSO according to the standard procedure, then the reaction mixture was quenched with methyl iodide. Gratifyingly, methylated target product **7da** was obtained in 58% yield. Furthermore, a slightly modified procedure involving a final quench with dimethyl sulfate produced **7da** in greater yields (88%) (Scheme 8). One-pot alkylation with in situ methylation of halogenated precursors **6ag** and **6ai** proceeded in the presence of dimethyl sulfate with comparable efficiency affording *N*-methylated products **7dg** and **7di**, respectively (Scheme 8). Also, benzylation with BnBr could be incorporated in the one-pot protocol to convert **6aa** into *N*-benzylated product **7ea** (Scheme 8). In a similar manner, allylation and propargylation could be performed in the presence of corresponding organic halides yielding *N*-allyl (**7ha**) and *N*-propargyl (**7ia**) derivatives, respectively (Scheme 8). The formation of an indoline-3-one moiety and successful incorporation of an *N*-allyl substituent into the structure of compound **7ha** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC # 2126910, see the Supporting Information for details).

Mechanistic rationale elucidating the formation of 2-(3-oxoindolin-2-ylidene)acetonitriles **1** is shown in Scheme 9. It is believed that the process begins with base-assisted deprotonation of the α-CH bond in ketone **6** to afford enolate **12**, which attacks a molecule of DMSO providing dimethylvinylsulfanol **13**. The acidic α-CH bond next to cyano function in this structure could also be deprotonated with KOH, followed by the elimination of dimethylsulfide and water to afford cyanochalcone **14**. In our recent report, we demonstrated similar oxidations of cyanoketones lacking *ortho*-aniline functionality.[20]

In the presence of such *ortho*-amino group, subsequent nucleophilic 5-*exo*-*trig* cyclization would render indoline-3-one **15**, which could then be deprotonated at the α-CH bond of the cyano group. The resulting cyclic enolate **16** could again react with DMSO providing dimethylvinylsulfanol **17**. The following deprotonation α-CH bond next to cyano function followed by the elimination of dimethylsulfide and water

Scheme 8. One-Pot Approach for the Preparation of *N*-Alkylated 2-(3-oxoindolin-2-ylidene)acetonitriles 7 from 4-(2-Aminophenyl)-4-oxo-2-phenylbutanenitriles 6



produces product **1** (Scheme 9). In a similar manner, secondary aniline **10** would afford *N*-substituted indoline **7**; however, there is a drastic difference in the postreaction behavior. The N−H bond in indoline-3-one **1** in the presence of excess base could be deprotonated, which dramatically decreases its electrophilicity. As a result, anionic species **18** is relatively persistent and could survive before being quenched with protic acid or S_N2-active organyl halide to afford products **1** or **7**, respectively (Scheme 10). Compound **7** generated from secondary aniline **10**, in the presence of excess base, cannot be deactivated via deprotonation. Consequently, it would suffer from the nucleophilic attack of hydroxide across the conjugated C═C bond to afford enolate **19**. Subsequent elimination of the cyano group would provide enol **20**, further tautomerizing into thermodynamically more stable form **11** (Scheme 10).

Finally, it was decided to explore how this methodology could be used to streamline the approach toward antimycobacterial pyridazino[4,3-*b*]indoles structures **2**, originally investigated by Velezheva.[16] Oxidative cyclization of 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitriles **6** was carried out as usual, but during the acidic quenching, hydrazide hydrate was added to the reaction mixture, which was boiled at reflux for 4 h. Gratifyingly, this one-pot sequence led to the

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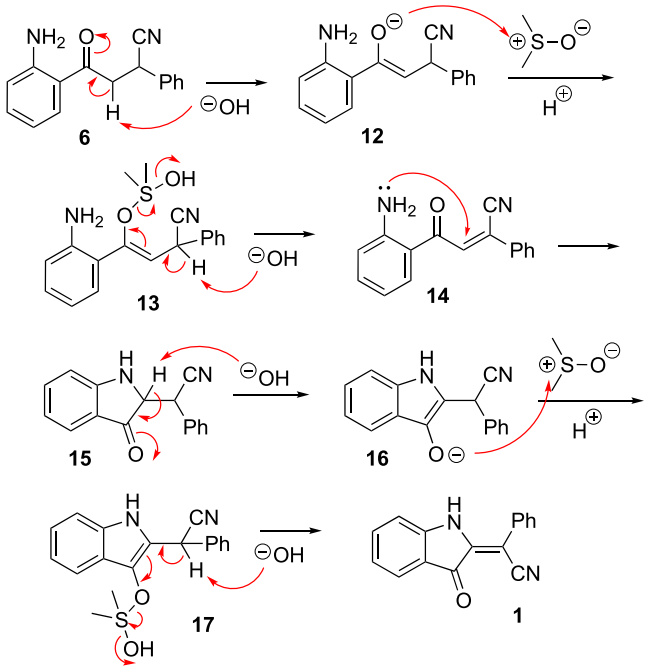
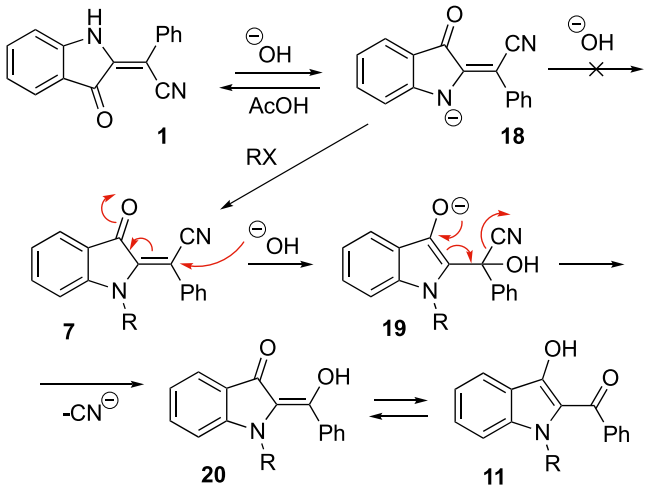
Scheme 9. Mechanistic Rationale for the Formation of Products 1

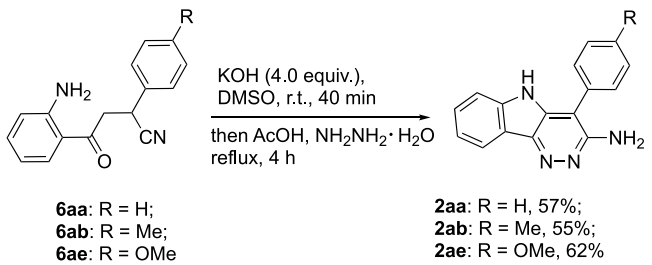


Scheme 10. Mechanistic Rationale for the Formation of Products 11



formation of the desired molecules 2 in good yields (Scheme 11).

Scheme 11. One-Pot Synthesis of Antimycobacterial Pyridazino[4,3-*b*]indoles 2



CONCLUSIONS

An improved synthetic approach toward 2-(3-oxoindolin-2-ylidene)acetonitriles **1** was developed. This method involves base-assisted cyclization of 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitriles **6** accompanied by oxidation with DMSO. It was shown that this reaction proceeds smoothly only for primary aniline derivatives **6**. Starting materials **10** possessing a secondary aniline group participated in a side reaction involving cleavage of the cyano group. However, an alternative access toward *N*-substituted indoline-3-ones **7** was also designed, employing in situ alkylation of indolines **1**. This methodology was used to design an expeditious one-pot approach toward pyridazino[4,3-*b*]indoles **2** with known antimycobacterial activities. Synthetic studies toward more complex polycyclic scaffolds taking advantage of this newly developed method are currently underway in our laboratories.

EXPERIMENTAL PART

General. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker Avance-III spectrometer (400 or 100 MHz, respectively) equipped with BBO probe in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. High-resolution mass spectra were registered with a Bruker Maxis spectrometer (electrospray ionization, in MeCN solution, using HCO_2Na−HCO_2H for calibration). Melting points were measured with a Stuart smp30 apparatus. All reactions were performed in oven-dried 3 mL Weaton microreactors equipped with magnetic spin-vane and Mininert valve, employing magnetic stirring. Reaction progress and purity of isolated compounds were controlled by thin-layer chromatography (TLC) on Silufol UV-254 plates, eluting with a 4:1 hexanes/EtOAc mixture. All 4-(2-aminophenyl)-4-oxo-2-arylbutanenitriles (**6**), except for compound **6ak**, were synthesized according to the procedure published in our recent report.[18] All other reagents and solvents were purchased from commercial vendors and used as received.

*4-Bromo-2′-aminochalcone (**9ak**).* This compound was prepared by the procedure described in the literature[21] employing 2′-aminoacetophenone (405 mg, 3 mmol) and 4-bromobenzaldehyde (552 mg, 3.00 mmol). The title compound was obtained as yellow solid, mp 101.7−102.8 °C (EtOH), lit[21] mp 94−96 °C (EtOH), R_f 0.44 (EtOAc/hexane, 1:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.4, 1.5 Hz, 1H), 7.66 (d, J = 15.5 Hz, 1H), 7.60 (d, J = 15.5 Hz, 1H), 7.56−7.52 (m, 2H), 7.51−7.47 (m, 2H), 7.30 (ddd, J = 8.5, 7.1, 1.5 Hz, 1H), 6.74−6.66 (m, 2H), 6.34 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 191.5, 151.2, 141.6, 134.6, 134.4, 132.3 (2C), 131.1, 129.8 (2C), 124.4, 123.8, 119.0, 117.5, 116.0; FTIR (film, NaCl, cm^{-1}): 3427, 3326, 2926, 1636, 1581, 1542, 1482, 1446, 1390, 1333, 1207, 1164, 1070, 1005; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{15}H_{12}BrNNaO$ 323.9994; found 323.9990 (1.4 ppm).

*(E)-1-(2-Amino-5-nitrophenyl)-3-phenylprop-2-en-1-one (**9ja**).* 1-(2-Amino-5-nitrophenyl)ethan-1-one[22] (540 mg, 3.00 mmol), benzaldehyde (318 mg, 3.00 mmol), and ethanol (15 mL) were placed in a 50 mL beaker. Then, 300 μL of 40% KOH was added and the mixture was left overnight, after which the formed precipitate was filtered off. The title compound was obtained as a yellow solid, mp 154.6−156.2 °C (EtOH), R_f 0.56 (EtOAc/hexane, 1:2). Yield 579 mg (2.16 mmol, 72%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 2.6 Hz, 1H), 8.46 (br. s, 2H), 8.12 (dd, J = 9.3, 2.6 Hz, 1H), 8.01 (d, J = 15.4 Hz, 1H), 7.94−7.88 (m, 2H), 7.71 (d, J =

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15.4 Hz, 1H), 7.47 (dd, J = 5.0, 1.9 Hz, 3H), 6.93 (d, J = 9.3 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 190.3, 156.4, 143.8, 135.1, 134.7, 130.6, 129.1 (2C), 129.0, 129.0, 129.0 (2C), 122.6, 117.2, 115.7; FTIR (film, NaCl, cm^{-1}): 3419, 3296, 1645, 1616, 1588, 1494, 1474, 1308, 1260, 1206, 1115; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{15}H_{12}N_2NaO_3$ 291.0740; found 291.0738 (0.8 ppm).

*4-(2-Aminophenyl)-2-(4-bromophenyl)-4-oxobutanenitrile (**6ak**).* This compound was prepared via a method previously described in the literature.[18] A 25 mL round-bottom flask was charged with 4-bromo-2′-aminochalcone (**9ak**) (1.34 g, 2.00 mmol), acetic acid (120 mg, 114 μL, 2.00 mmol), and DMSO (6 mL). The mixture was vigorously stirred, and a solution of KCN (260 mg, 4.00 mmol) in water (0.5 mL) was added dropwise. Then, the reaction vessel was equipped with a reflux condenser, and the mixture was stirred at 50 °C for 1 h, while the reaction progress was monitored by TLC. Upon complete conversion, the mixture was diluted with water (30 mL) and extracted with dichloromethane (4 × 15 mL). Combined organic extracts were washed with water (4 × 15 mL), concentrated in vacuum, and purified by preparative column chromatography on silica gel eluting with 1:4 EtOAc/hexane. The title compound was obtained as a yellow solid, mp 105.1−106.0 °C (EtOH), R_f 0.24 (EtOAc/hexane, 1:4). Yield 315 mg (0.96 mmol, 48%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 8.2, 1.5 Hz, 1H), 7.56−7.48 (m, 2H), 7.34−7.26 (m, 3H), 6.66 (dd, J = 8.4, 1.1 Hz, 1H), 6.62 (ddd, J = 8.2, 7.1, 1.2 Hz, 1H), 6.29 (s, 2H), 4.51 (dd, J = 7.9, 6.1 Hz, 1H), 3.68 (dd, J = 17.5, 7.9 Hz, 1H), 3.46 (dd, J = 17.6, 6.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 195.7, 150.8, 135.3, 134.7, 132.5 (2C), 130.5, 129.4 (2C), 122.5, 120.6, 117.7, 116.7, 116.1, 44.7, 31.7; FTIR (film, NaCl, cm^{-1}): 3470, 3355, 2930, 2246, 1643, 1612, 1571, 1547, 1489, 1453, 1248, 1171, 1072; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{16}H_{13}BrN_2NaO$ 351.0103; found 351.0095 (2.4 ppm).

*4-(2-Amino-5-nitrophenyl)-4-oxo-2-phenylbutanenitrile (**6ja**).* This compound was prepared in analogy to the method described for **6ak** employing (*E*)-1-(2-amino-5-nitrophenyl)-3-phenylprop-2-en-1-one (**9ja**) (536 mg, 2 mmol). The title compound was obtained as a yellow solid, mp 183.9−186.0 °C (EtOH), R_f 0.44 (EtOAc/hexane, 1:2). Yield 572 mg (1.94 mmol, 97%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 2.6 Hz, 1H), 8.36 (s, 2H), 8.09 (dd, J = 9.4, 2.6 Hz, 1H), 7.60−7.48 (m, 2H), 7.46−7.39 (m, 2H), 7.39−7.33 (m, 1H), 6.90 (d, J = 9.4 Hz, 1H), 4.56 (dd, J = 9.1, 5.0 Hz, 1H), 4.09 (dd, J = 18.2, 9.2 Hz, 1H), 3.80 (dd, J = 18.2, 5.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 197.2, 155.6, 135.8, 134.9, 129.4, 129.1, 128.9 (2C), 128.0, 127.9 (2C), 121.5, 117.4, 113.8, 43.0, 31.2; FTIR (film, NaCl, cm^{-1}): 3464, 3356, 2242, 1657, 1616, 1558, 1484, 1310, 1274, 1264, 1246, 1109; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{16}H_{13}N_3NaO_3$ 318.0849; found 318.0848 (0.4 ppm).

*4-(2-(Methylamino)phenyl)-2-phenyl-4-oxobutyronitrile (**10da**).* 4-(2-Aminophenyl)-4-oxo-2-phenylbutanenitrile[18] (**6aa**) (1.25 g, 5.00 mmol), MeCN (3 mL), Me_2SO_4 (1.26 g, 0.95 mL, 10.0 mmol), and K_2CO_3 (1.38 g, 10.0 mmol) were placed in a 25 mL round-bottom flask equipped with a magnetic stirring bar and allowed to reflux to 1.5 h. After consumption of the starting material, the resulting solution was poured out into a separating funnel filled with water (50 mL), $NaHCO_3$ (0.84 g, 10 mmol), and CH_2Cl_2 (50 mL). The aqueous layer was discarded and the organic layer washed with saturated $NaHCO_3$ solution (2 × 30 mL). Next, the solution was concentrated in vacuo and purified by column chromatography eluting with benzene. The title compound was isolated as an orange oil, R_f 0.40 (EtOAc/hexane, 1:4). Yield 726 mg (2.75 mmol, 55%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 7.61 (dd, J = 8.2, 1.6 Hz, 1H), 7.47−7.29 (m, 6H), 6.71 (dd, J = 8.6, 1.1 Hz, 1H), 6.56 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 4.51 (dd, J = 8.6, 5.6 Hz, 1H), 3.71 (dd, J = 17.5, 8.6 Hz, 1H), 3.49 (dd, J = 17.5, 5.6 Hz, 1H), 2.93 (d, J = 5.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.1, 152.4, 135.8, 135.7, 131.2, 129.3 (2C), 128.4, 127.6 (2C), 121.1, 116.2, 114.2, 111.8, 44.8, 32.3, 29.5; FTIR (film, NaCl, cm^{-1}): 3340, 2926, 2246, 1631, 1569, 1520, 1424, 1251, 1202, 1166; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{17}H_{16}N_2NaO$ 287.1151; found 287.1155 (1.3 ppm).

*2-(4-Methoxyphenyl)-4-(2-(methylamino)phenyl)-4-oxobutanenitrile (**10de**).* This compound was prepared via the published method used for the preparation of **10da** employing 4-(2-aminophenyl)-2-(4-methoxyphenyl)-4-oxobutanenitrile[18] (**6ae**) (1.40 g, 5.00 mmol) and Me_2SO_4 (1.26 g, 0.95 mL, 10.0 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:4. The title compound was obtained as a yellow oil, R_f 0.35 (EtOAc/hexane, 1:4). Yield 779 mg (2.65 mmol, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (br. s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.33 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.6 Hz, 1H), 6.56 (t, J = 7.6 Hz, 1H), 4.46 (dd, J = 8.4, 5.8 Hz, 1H), 3.81 (s, 3H), 3.67 (dd, J = 17.4, 8.3 Hz, 1H), 3.46 (dd, J = 17.4, 5.8 Hz, 1H), 2.92 (d, J = 5.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.2, 159.5, 152.4, 135.8, 131.2, 128.8 (2C), 127.5, 121.4, 116.2, 114.7 (2C), 114.2, 111.7, 55.5, 44.8, 31.5, 29.4; FTIR (film, NaCl, cm^{-1}): 3350, 2940, 2246, 1634, 1566, 1513, 1424, 1248, 1173, 1029; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{18}H_{18}N_2NaO_2$ 317.1260; found 317.1258 (0.7 ppm).

*4-(2-(Benzylamino)phenyl)-4-oxo-2-phenylbutanenitrile (**10ea**).* This compound was prepared via the published method used for the preparation of **6da** employing 4-(2-aminophenyl)-2-(4-methoxyphenyl)-4-oxobutanenitrile[18] (**6ae**) (1.4 g, 5 mmol) and benzyl bromide (1.71 g, 1.19 mL, 10.0 mmol). Eluent for preparative column chromatography: benzene. The title compound was obtained as an orange solid, mp 121.2−122.2 °C (EtOH), R_f 0.44 (EtOAc/hexane, 1:4). Yield 1.02 g (3.00 mmol, 60%). ^1H NMR (400 MHz, DMSO-d_6) δ 9.27 (t, J = 5.9 Hz, 1H), 7.65 (dd, J = 8.2, 1.6 Hz, 1H), 7.48−7.27 (m, 11H), 6.68 (d, J = 8.6 Hz, 1H), 6.58 (t, J = 7.6 Hz, 1H), 4.53 (dd, J = 8.7, 5.5 Hz, 1H), 4.48 (d, J = 5.7 Hz, 2H), 3.75 (dd, J = 17.5, 8.7 Hz, 1H), 3.50 (dd, J = 17.5, 5.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.3, 151.4, 138.5, 135.8, 135.7, 131.3, 129.4 (2C), 128.9 (2C), 128.4, 127.6 (2C), 127.4, 127.1 (2C), 121.1, 116.5, 114.8, 112.7, 46.9, 45.0, 32.4; FTIR (film, NaCl, cm^{-1}): 3326, 2241, 1631, 1571, 1518, 1453, 1255, 1195, 1055; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{23}H_{20}N_2NaO$ 363.1468; found 363.1457 (3.0 ppm).

*N-(2-(3-Cyano-3-phenylpropanoyl)phenyl)acetamide (**10fa**).* 4-(2-Aminophenyl)-4-oxo-2-phenylbutanenitrile[18] (**6aa**) (1.00 g, 4.00 mmol), CH_2Cl_2 (4 mL), and Et_3N (444 mg, 317 μL, 4.40 mmol) were placed in a 25 mL round-bottom flask equipped with a magnetic stirring bar. Then, AcCl (377 mg, 343 μL, 4.80 mmol) was added maintaining the reaction mixture temperature below 30 °C and stirred for 3 h. After consumption of starting material, the resulting solution was partitioned between water (50 mL) and CH_2Cl_2 (50 mL). The

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aqueous layer was discarded, and the organic layer washed with saturated $NaHCO_3$ solution (2 × 30 mL). Next, the solution was concentrated in vacuo and purified by column chromatography (eluting with ethyl acetate/hexane 1:2 v/v) or by recrystallization from benzene. The title compound was obtained as a colorless solid, m.p. = 113.7−115.6 (benzene), R_f 0.44 (EtOAc/Hex, 1:2). Yield 1.121 g (3.84 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 8.82−8.68 (m, 1H), 7.78 (dd, J = 8.2, 1.6 Hz, 1H), 7.56 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 7.48−7.30 (m, 5H), 7.12−7.00 (m, 1H), 4.47 (dd, J = 8.9, 5.2 Hz, 1H), 3.79 (dd, J = 18.0, 8.8 Hz, 1H), 3.54 (dd, J = 18.0, 5.3 Hz, 1H), 2.25 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.8, 169.6, 141.5, 136.0, 134.9, 130.4, 129.5 (2C), 128.7, 127.5 (2C), 122.5, 121.1, 120.6, 120.5, 45.8, 32.2, 25.7; FTIR (film, NaCl, cm^{-1}): 3258, 2964, 2251, 1694, 1660, 1585, 1537, 1448, 1354, 1293, 1243, 1190; HRMS (ESI TOF) calc'd for $C_{18}H_{16}N_2NaO_2$ $(M + Na)^+$ 315.1104, found 315.1100 (1.3 ppm).

*(E)-2-(3-Oxoindolin-2-ylidene)-2-phenylacetonitrile (**1aa**). Typical Procedure A for the Synthesis of (E)-2-(3-Oxoindolin-2-ylidene)-2-arylacetonitriles **1**.* 4-(2-Aminophenyl)-4-oxobutyronitrile[18] (**6aa**) (125 mg, 0.50 mmol), DMSO (0.4 mL), and KOH (112 mg, 2.00 mmol) were mixed in a 5 mL round-bottom flask and stirred at room temperature for 30−40 min. Saturated green color of the reaction mixture quickly developed, which may indicate peroxidation. Next, AcOH (0.2 mL) was added and the mixture was stirred for another 30 min, during which the reaction product usually precipitated. The reaction was diluted with 60 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ solution (3 × 10 mL). Next, the solution was concentrated and the residual oil was purified by column chromatography (eluting with ethyl acetate/hexane 1:2 v/v) or by recrystallization from ethanol. Yield 95 mg (0.39 mmol, 77%). The same compound was prepared starting from *N*-(2-(3-cyano-3-phenylpropanoyl)-phenyl)acetamide (**10fa**) (146 mg, 0.50 mmol) with yield 79 mg (0.32 mmol, 64%). Alternatively, this compound was prepared starting from *N*-(2-(3-cyano-3-phenylpropanoyl)-phenyl)-4-methylbenzenesulfonamide[18] (**10ga**) (202 mg, 0.50 mmol) in a yield of 83 mg (0.34 mmol, 67%). All physical data were identical to those previously described.[17] R_f 0.65 (EtOAc/Hex, 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (br. s, 1H), 7.68−7.61 (m, 3H), 7.57 (t, J = 7.6 Hz, 3H), 7.48 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.2, 152.5, 142.5, 137.4, 132.1, 129.3 (2C), 129.1, 128.8 (2C), 124.9, 121.4, 119.5, 118.0, 112.7, 88.8; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{16}H_{10}N_2NaO$ 269.0685; found 269.0693 (−3.0 ppm).

*Typical Procedure B for the Synthesis of (E)-2-(3-Oxoindolin-2-ylidene)-2-arylacetonitriles **1** (Scale-Up Procedure).* 4-(2-Aminophenyl)-4-oxobutyronitrile[18] (**6aa**) (0.50 g, 2.00 mmol), DMSO (1.6 mL), and KOH (448 mg, 8.00 mmol) were mixed in a 5 mL round-bottom flask and left for 30−40 min under stirring at room temperature. A saturated green color of the reaction mixture quickly developed, which may indicate peroxidation. Next, AcOH (0.8 mL) was added and the mixture was stirred for another 30 min, during which the reaction product usually precipitated. The reaction was diluted with CH_2Cl_2 (240 mL) and washed with saturated solution of $NaHCO_3$ (3 × 40 mL). Next, the solution was concentrated and purified by column chromatography (eluent ethyl acetate:hexane 1:2 v/v) or by recrystallization from alcohol. Yield 389 mg (1.58 mmol, 79%). The obtained sample is identical to that obtained by typical procedure A.

*(E)-2-(3-Oxoindolin-2-ylidene)-2-(p-tolyl)acetonitrile (**1ab**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-4-oxo-2-(*p*-tolyl)butanenitrile[18] (**6ab**) (132 mg, 0.5 mmol). Eluent for preparative column chromatography:EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.46 (EtOAc/hexane, 1:4). Yield 117 mg (0.45 mmol, 90%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.62−7.45 (m, 3H), 7.38 (d, J = 7.8 Hz, 2H), 7.09 (d, J = 8.1 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 2.38 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.2, 152.5, 142.1, 139.0, 137.4, 130.0 (2C), 129.2, 128.7 (2C), 124.8, 121.4, 119.5, 118.0, 112.7, 89.2, 20.9; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{17}H_{12}N_2NaO$ 283.0842; found 283.0845 (−1.0 ppm).

*(E)-2-(4-Ethylphenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1ac**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(4-ethylphenyl)-4-oxobutanenitrile[18] (**6ac**) (139 mg, 0.50 mmol). Eluent for preparative column chromatography:EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.56 (EtOAc/Hex, 1:2). Yield 116 mg (0.42 mmol, 85%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.45 (br. s, 1H), 7.64 (dt, J = 7.6, 0.9 Hz, 1H), 7.62−7.53 (m, 3H), 7.44−7.38 (m, 2H), 7.09 (d, J = 8.0 Hz, 1H), 7.01 (td, J = 7.5, 0.9 Hz, 1H), 2.68 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.1, 152.5, 145.2, 142.1, 137.4, 129.4, 128.8 (2C), 128.8 (2C), 124.8, 121.4, 119.5, 118.0, 112.7, 89.2, 28.0, 15.4; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{18}H_{14}N_2NaO$ 297.0998; found 297.0994 (1.5 ppm).

*(E)-2-(4-Isopropylphenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1ad**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(4-isopropylphenyl)-4-oxobutanenitrile[18] (**6ad**) (146 mg, 0.50 mmol). Eluent for preparative column chromatography:EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.47 (EtOAc/Hex, 1:2). Yield 83 mg (0.29 mmol, 58%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.62−7.51 (m, 3H), 7.47−7.40 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 7.02 (td, J = 7.4, 0.7 Hz, 1H), 3.04−2.86 (m, 1H), 1.25 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.6, 152.9, 150.2, 142.6, 137.8, 130.0 (2C), 129.3 (2C), 127.8, 127.8, 125.3, 121.8, 120.0, 118.4, 113.2, 89.6, 33.8, 24.1; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{19}H_{16}N_2NaO$ 311.1555; found 311.1148 (2.2 ppm).

*(E)-2-(4-Methoxyphenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1ae**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(4-methoxyphenyl)-4-oxobutanenitrile[18] (**6ae**) (140 mg, 0.50 mmol). Eluent for preparative column chromatography:EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.43 (EtOAc/Hex, 1:2). Yield 106 mg (0.39 mmol, 77%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) 10.40 (s, 1H), 7.78−7.43 (m, 4H), 7.21−7.05 (m, 3H), 7.01 (t, J = 7.4 Hz, 1H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.5, 160.3, 152.9, 142.0, 137.7, 130.0 (2C), 125.2, 124.5, 121.7, 120.1, 118.5, 115.3 (2C), 113.2, 89.9, 55.9; HRMS (ESI

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TOF) m/z: (M + Na)$^+$ calc'd for $C_{17}H_{12}N_2NaO_2$ 299.0791; found 299.0784 (2.3 ppm).

*(E)-2-(2-Methoxyphenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1af**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(2-methoxyphenyl)-4-oxobutanenitrile[18] (**6af**) (140 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as an orange solid, mp 261.5−263.1 °C (EtOH), R_f 0.28 (EtOAc/hexane, 1:2). Yield 60 mg (0.21 mmol, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.58−7.46 (m, 2H), 7.43 (d, J = 7.5 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 8.2 Hz, 2H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.4, 157.3, 152.7, 143.8, 138.0, 131.6, 131.3, 125.3, 121.6, 121.5, 120.4, 119.9, 118.2, 112.8, 112.7, 86.3, 56.2; FTIR (film, NaCl, cm^{-1}): 3268, 2212, 1701, 1605, 1484, 1462, 1330, 1212, 1142; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{17}H_{12}N_2NaO$ 299.0791; found 299.0801 (3.5 ppm).

*(E)-2-(4-Fluorophenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1ag**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(4-fluorophenyl)-4-oxobutanenitrile[18] (**6ag**) (134 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.54 (EtOAc/hexane, 1:4). Yield 94 mg (0.36 mmol, 71%). All physical data identical to previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (s, 1H), 7.79−7.62 (m, 3H), 7.58 (t, J = 7.8 Hz, 1H), 7.48−7.33 (m, 2H), 7.08 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.6, 162.6 (d, J = 247.9 Hz), 152.9, 143.1, 138.0, 131.7 (d, J = 8.7 Hz, 2C), 128.9 (d, J = 3.2 Hz), 125.4, 122.0, 120.0, 118.4, 116.8 (d, J = 22.0 Hz, 2C), 113.1, 88.3; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{16}H_9FN_2NaO$ 287.0591; found 287.0600 (−3.0 ppm).

*(E)-2-(2-Fluorophenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1ah**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(2-fluorophenyl)-4-oxobutanenitrile[18] (**6ah**) (134 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.63 (EtOAc/hexane, 1:1). Yield 110 mg (0.42 mmol, 83%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 7.69−7.52 (m, 4H), 7.48−7.31 (m, 2H), 7.02 (t, J = 7.6 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.4, 159.8 (d, J = 249.7 Hz), 152.7, 144.7, 138.3, 132.3 (d, J = 8.5 Hz), 131.9 (d, J = 2.5 Hz), 125.8 (d, J = 3.4 Hz), 125. 6, 122.1, 119.9 (d, J = 14.7 Hz), 119.8, 117.1 (d, J = 20.9 Hz), 117.0, 112.9, 82.4; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{16}H_9FN_2NaO$ 287.0591; found 287.0583 (2.8 ppm).

*(E)-2-(4-Chlorophenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1ai**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(4-chlorophenyl)-4-oxobutanenitrile[18] (**6ai**) (142 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.22 (EtOAc/hexane, 1:2). Yield 115 mg (0.41 mmol, 82%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.70−7.55 (m, 6H), 7.07 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.2, 152.4, 142.9, 137.6, 133.7, 131.0, 130.8 (2C), 129.4 (2C), 125.0, 121.7, 119.5, 117.8, 112.7, 87.5; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{16}H_9ClN_2NaO$ 303.0296; found 303.0292 (1.1 ppm).

*(E)-2-(3-Chlorophenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1aj**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(3-chlorophenyl)-4-oxobutanenitrile[18] (**6aj**) (142 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.57 (EtOAc/hexane, 1:2). Yield 67 mg (0.24 mmol, 48%). All physical data were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.72−7.62 (m, 2H), 7.64−7.51 (m, 4H), 7.09 (d, J = 8.0 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.2, 152.4, 143.1, 137.6, 134.2, 133.9, 131.1, 129.0, 128.5, 127.6, 125.0, 121.7, 119.4, 117.7, 112.7, 87.0; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{16}H_9ClN_2NaO$ 303.0296; found 303.0292 (1.2 ppm).

*(E)-2-(4-Bromophenyl)-2-(3-oxoindolin-2-ylidene)-acetonitrile (**1ak**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-2-(4-bromophenyl)-4-oxobutanenitrile[18] (**6ak**) (164 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.66 (EtOAc/hexane, 1:2). Yield 141 mg (0.44 mmol, 87%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 3H), 7.07 (d, J = 8.0 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 184.2, 152.4, 142.9, 137.6, 132.3 (2C), 131.4, 130.9 (2C), 125.0, 122.4, 121.6, 119.4, 117.7, 112.7, 87.5; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{16}H_9N_2NaO$ 346.9790; found 346.9788 (0.8 ppm).

*(E)-2-(3-Oxoindolin-2-ylidene)-2-(pyridin-2-yl)acetonitrile (**1al**).* This compound was prepared by typical procedure A employing 4-(2-aminophenyl)-4-oxo-2-(pyridin-2-yl)-butanenitrile[18] (**6al**) (146 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.36 (EtOAc/Hex, 1:2). Yield 104 mg (0.42 mmol, 84%). All physical properties were identical to those previously described.[17] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 8.76 (d, J = 4.9 Hz, 1H), 7.99 (t, J = 7.8 Hz, 1H), 7.80 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.60 (t, J = 7.7 Hz, 1H), 7.49−7.31 (m, 2H), 7.05 (t, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 185.6, 152.8, 152.3, 149.6, 143.6, 138.4, 138.0, 125.4, 123.1, 122.9, 122.6, 119.6, 117.0, 113.9, 85.4; HRMS (ESI TOF) m/z: (M + Na)$^+$ calc'd for $C_{15}H_9N_3NaO$ 270.0638; found 270.0645 (−2.7 ppm).

*(E)-2-(5-Bromo-3-oxoindolin-2-ylidene)-2-phenylacetonitrile (**1ba**).* This compound was prepared by typical procedure A employing 4-(2-amino-5-bromophenyl)-4-oxo-2-phenylbutanenitrile[18] (**6ba**) (164 mg, 00.5 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a dark red solid, mp 261.5−263.1 °C (EtOH), R_f 0.5 (EtOAc/hexane, 1:2). Yield 142 mg (0.44 mmol, 88%). Yield mg (4.32 mmol, 72%). All physical data were identical to those previously described.[16] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 8.6, 2.1 Hz, 1H), 7.67−7.62 (m, 2H), 7.61−7.55 (m, 2H), 7.53−7.47 (m, 1H), 7.06 (d, J = 8.5 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 183.4, 151.8,

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142.7, 139.9, 132.3, 129.9 (2C), 129.8, 129.3 (2C), 127.5, 121.8, 118.2, 115.3, 113.5, 90.4; FTIR (film, NaCl, cm^{-1}): 3321, 2202, 1708, 1600, 1465, 1316, 1272, 1217, 1166, 1120; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{16}H_9BrN_2NaO$ 346.9790; found 346.9787 (0.9 ppm).

*(E)-2-(5,6-Dimethoxy-3-oxoindolin-2-ylidene)-2-phenylacetonitrile (**1ca**).* This compound was prepared by typical procedure A employing 4-(2-amino-4,5-dimethoxyphenyl)-4-oxo-2-phenylbutanenitrile[18] (**6ca**) (155 mg, 0.50 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, R_f 0.47 (EtOAc/hexane, 1:1). Yield 69 mg (0.23 mmol, 45%). All physical data identical to those previously described.[17] ^1H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 7.62 (d, J = 7.1 Hz, 2H), 7.55 (t, J = 7.6 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.07 (s, 1H), 6.62 (s, 1H), 3.85 (s, 3H), 3.75 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 181.9, 157.8, 150.2, 144.9, 143.9, 132.2, 129.3 (2C), 129.0, 128.8 (2C), 118.0, 110.4, 105.8, 95.9, 88.5, 56.1, 55.9; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{18}H_{14}N_2NaO_3$ 329.0897; found 329.0887 (2.8 ppm).

*(E)-2-(3-Oxoindolin-2-ylidene)-2-(p-tolyl)acetonitrile (**1ja**).* This compound was prepared by typical procedure A employing 4-(2-amino-5-nitrophenyl)-4-oxo-2-phenylbutanenitrile (**6ja**) (148 mg, 0.5 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:1. The title compound was obtained as a yellow solid, mp 269.1−271.6 °C (EtOH), R_f 0.41 (EtOAc/hexane, 1:1). Yield 62 mg (0.21 mmol, 42%). ^1H NMR (400 MHz, DMSO-d_6) δ 11.25 (s, 1H), 8.43 (dd, J = 8.8, 2.4 Hz, 1H), 8.39 (d, J = 2.3 Hz, 1H), 7.71−7.64 (m, 2H), 7.63−7.57 (m, 2H), 7.57−7.50 (m, 1H), 7.23 (d, J = 8.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 182.8, 156.0, 142.8, 141.4, 132.4, 131.5, 129.8, 129.5 (2C), 129.0 (2C), 120.8, 119.7, 117.4, 113.1, 92.4; FTIR (film, NaCl, cm^{-1}): 3272, 3101, 3065, 2215, 1709, 1628, 1606, 1590, 1521, 1474, 1455, 1344, 1318, 1250, 1208, 1134; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{16}H_9N_3NaO_3$ 314.0536; found 314.0534 (0.8 ppm).

*(E)-2-(1-Methyl-3-oxoindolin-2-ylidene)-2-phenylacetonitrile (**7da**). Typical Procedure C for the Synthesis of (E)-2-(1-Alkyl-3-oxoindolin-2-ylidene)-2-arylacetonitriles **7** from 4-(2-Aminophenyl)-4-oxo-2-arylbutanenitriles **6**.* 4-(2-Aminophenyl)-2-phenyl-4-oxobutyronitrile[18] (**6aa**) (125 mg, 0.50 mmol), DMSO (0.2 mL), and KOH (56 mg, 1.0 mmol) were mixed in a 5 mL round-bottom flask and left for 30−40 min under stirring at room temperature. Next, an alkylating agent was added and the mixture was left for another 5 min (TLC control), after which the reaction was immediately diluted with 60 mL of CH_2Cl_2 and washed (3 × 10 mL) with saturated $NaHCO_3$ solution. Next, the solution was evaporated and purified by column chromatography (eluent ethyl acetate:hexane 1: 2 v/v) or by recrystallization from ethyl alcohol. When Me_2SO_4 (126 mg, 95 μL, 1.00 mmol) was used, the yield was 114 mg (0.44 mmol, 88%). When MeI (142 mg, 62 μL, 1.00 mmol) was used, the yield was 75 mg (0.29 mmol, 58%). All physical data were identical to those previously described.[16] The title compound was obtained as a red solid, mp 149.0−151.2 °C (MeOH), R_f 0.33 (EtOAc/hexane, 1:2). Yield mg (4.32 mmol, 72%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.74−7.60 (m, 2H), 7.57−7.42 (m, 5H), 7.20 (d, J = 8.1 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 2.81 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 184.0, 154.2, 144.4, 137.5, 132.4, 130.1 (2C), 129.1, 128.7 (2C), 124.6, 121.9, 119.6, 118.8, 110.8, 89.3, 33.7; FTIR (film, NaCl, cm^{-1}): 2983, 2193, 1708, 1617, 1581, 1475, 1361, 1328, 1248, 1198, 1164, 1130, 1104, 1026, 973; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{17}H_{12}N_2NaO$ 283.0842; found 283.0833 (3.0 ppm).

*Typical Procedure D for the Synthesis of (E)-2-(1-Alkyl-3-oxoindolin-2-ylidene)-2-arylacetonitriles **7** from 4-(2-(Methylamino)phenyl)-4-oxo-2-arylbutanenitriles **10**.* 4-(2-(Methylamino)phenyl)-2-phenyl-4-oxobutyronitrile[18] (**10da**) (125 mg, 0.50 mmol), DMSO (0.4 mL), and KOH (112 mg, 2 mmol) were mixed in a 5 mL round-bottom flask and left for 10 min under stirring at room temperature. AcOH (0.2 mL) was added and, then, the reaction was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (4 × 15 mL). Next, the solution was evaporated and purified by column chromatography (eluting with ethyl acetate/hexane 1:2 v/v) or by recrystallization from alcohol. Yield 20 mg (0.08 mmol, 15%). The obtained sample is identical to that obtained via typical procedure C.

*Typical Procedure E for the Synthesis of (E)-2-(1-Alkyl-3-oxoindolin-2-ylidene)-2-arylacetonitriles **7** from 4-(2-Aminophenyl)-4-oxo-2-arylbutanenitriles **6** (Scale-Up Procedure).* 4-(2-Aminophenyl)-2-phenyl-4-oxobutyronitrile[18] (**6aa**) (500 mg, 2.00 mmol), DMSO (0.8 mL), and KOH (224 mg, 4.00 mmol) were mixed in a 25 mL round-bottom flask and left for 30−40 min under stirring at room temperature. Next, Me_2SO_4 (504 mg, 380 μL, 4.00 mmol) was added and the mixture was left for another 5 min (TLC control), after which the reaction was immediately diluted with 240 mL of CH_2Cl_2 and washed (3 × 40 mL) with saturated $NaHCO_3$ solution. Next, the solution was evaporated and purified by column chromatography (eluting with ethyl acetate/hexane 1:2 v/v) or by recrystallization from ethyl alcohol. Yield 442 mg (1.70 mmol, 85%). The isolated sample was identical to that obtained via typical procedure C.

*(E)-2-(4-Fluorophenyl)-2-(1-methyl-3-oxoindolin-2-ylidene)acetonitrile (**7dg**).* This compound was prepared by typical procedure C employing 4-(2-aminophenyl)-2-(4-fluorophenyl)-4-oxobutanenitrile[18] (**6ag**) (134 mg, 0.50 mmol) and Me_2SO_4 (126 mg, 95 μL, 1.00 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, mp 170.8−174.1 °C (EtOH), R_f 0.67 (EtOAc/hexane, 1:1). Yield 107 mg (0.39 mmol, 77%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.73−7.62 (m, 2H), 7.61−7.54 (m, 2H), 7.40−7.32 (m, 2H), 7.22 (d, J = 8.1 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 2.82 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 184.1, 162.3 (d, J = 247.5 Hz), 154.2, 144.7, 132.5 (d, J = 8.7 Hz), 132.4, 128.9 (d, J = 3.3 Hz, 2C), 124.7, 122.1, 119.6, 118. 9, 115.9 (d, J = 22.0 Hz, 2C), 111.0, 88.2, 33.8; FTIR (film, NaCl, cm^{-1}): 3081, 2199, 1707, 1626, 1572, 1502, 1475, 1330, 1242, 1127; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{17}H_{11}FN_2NaO$ 301.0748; found 301.0749 (−0.3 ppm).

*(E)-2-(4-Chlorophenyl)-2-(1-methyl-3-oxoindolin-2-ylidene)acetonitrile (**7di**).* This compound was prepared by typical procedure C employing 4-(2-aminophenyl)-2-(4-chlorophenyl)-4-oxobutanenitrile[18] (**6ai**) (142 mg, 0.50 mmol) and Me_2SO_4 (126 mg, 95 μL, 1.00 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, mp 172.4−174.5 °C (EtOH), R_f 0.44 (EtOAc/hexane, 1:1). Yield 98 mg (0.34 mmol, 67%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.73−7.61 (m, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.1 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 2.84 (s,

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3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 184.1, 154.2, 144.8, 137.7, 133.8, 132.0 (2C), 131.5, 128.8 (2C), 124.7, 122.1, 119.6, 118.7, 111.0, 87.8, 34.0; FTIR (film, NaCl, cm^{-1}): 3061, 2194, 1701, 1612, 1586, 1470, 1362, 1322, 1126; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{17}H_{11}ClN_2NaO$ 317.0452; found 317.0454 (−0.7 ppm).

*(E)-2-(1-Benzyl-3-oxoindolin-2-ylidene)-2-phenylacetonitrile (**7ea**).* This compound was prepared by typical procedure C employing 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitrile[18] (**6aa**) (125 mg, 0.5 mmol) and benzyl bromide (94 mg, 65 μL, 0.55 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, mp 166.9−169.0 °C (EtOH), R_f 0.53 (EtOAc/hexane, 1:2). Yield 129 mg (0.39 mmol, 77%). All physical data were identical to those previously described.[16] ^1H NMR (400 MHz, DMSO-d_6) δ 7.76 (dd, J = 7.6, 1.3 Hz, 1H), 7.62 (ddd, J = 8.5, 7.3, 1.4 Hz, 1H), 7.44−7.30 (m, 5H), 7.21−7.14 (m, 4H), 7.12 (t, J = 7.4 Hz, 1H), 6.83−6.73 (m, 2H), 4.65 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 183.9, 153.7, 143.5, 137.7, 135.3, 132.0, 129.9 (2C), 129.5, 128.7 (2C), 128.5 (2C), 127.3, 125.9 (2C), 125.0, 122.3, 119.9, 118.8, 111.5, 90.8, 47.5; FTIR (film, NaCl, cm^{-1}): 3036, 2188, 1735, 1713, 1622, 1583, 1467, 1342, 1241, 1181, 1111; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{23}H_{16}N_2NaO$ 359.1155; found 359.1147 (2.2 ppm).

*(E)-2-(1-Allyl-3-oxoindolin-2-ylidene)-2-phenylacetonitrile (**7ha**).* This compound was prepared by typical procedure C 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitrile[18] (**6aa**) (125 mg, 0.50 mmol) and allyl bromide (61 mg, 43 μL, 0.55 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, mp 139.6−143.8 °C (EtOH), R_f 0.50 (EtOAc/hexane, 1:2). Yield 92 mg (0.32 mmol, 64%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 7.6 Hz, 1H), 7.70−7.60 (m, 1H), 7.55−7.46 (m, 5H), 7.20 (d, J = 8.2 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 5.58−5.31 (m, 1H), 5.03 (dt, J = 10.3, 1.4 Hz, 1H), 4.86 (dt, J = 17.1, 1.3 Hz, 1H), 3.96 (d, J = 4.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 184.0, 153.5, 143.5, 137.6, 132.3, 131.1, 129.9 (2C), 129.6, 128.9 (2C), 124.9, 122.2, 119.9, 118.8, 117.5, 111.6, 90.5, 46.6; FTIR (film, NaCl, cm^{-1}): 3082, 2178, 1703, 1582, 1472, 1443, 1346, 1193, 1105; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{19}H_{14}N_2NaO$ 309.0998; found 309.1004 (−1.8 ppm).

*(E)-2-(3-Oxo-1-(prop-2-yn-1-yl)indolin-2-ylidene)-2-phenylacetonitrile (**7ia**).* This compound was prepared by typical procedure C employing 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitrile[18] (**6aa**) (125 mg, 0.50 mmol) and propargyl bromide (65 mg, 42 μL, 0.55 mmol). Eluent for preparative column chromatography: EtOAc/hexane, 1:2. The title compound was obtained as a red solid, mp 169.7−171.4 °C (EtOH), R_f 0.47 (EtOAc/hexane, 1:2). Yield 88 mg (0.31 mmol, 62%). ^1H NMR (400 MHz, DMSO-d_6) δ 7.83−7.68 (m, 2H), 7.62−7.47 (m, 5H), 7.39 (d, J = 8.1 Hz, 1H), 7.19 (t, J = 7.4 Hz, 1H), 4.14 (d, J = 2.4 Hz, 2H), 3.23 (d, J = 2.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 183.7, 153.2, 143.4, 137.8, 131.8, 129.9 (2C), 129.9, 129.1 (2C), 125.0, 122.9, 120.5, 118.3, 112.0, 92.3, 77.2, 75.7, 35.0; FTIR (film, NaCl, cm^{-1}): 3264, 2195, 1707, 1590, 1477, 1435, 1336, 1186, 1111; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{19}H_{12}N_2NaO$ 307.0842; found 307.0838 (1.3 ppm).

*1-Methyl-2-benzoyl-3-hydroxyindole (**11da**). Typical Procedure F for the Preparation of 2-Aryloyl-3-hydroxyindoles **11** from 4-(2-Aminophenyl)-4-oxobutyronitriles **6**.* 4-(2-Aminophenyl)-2-phenyl-4-oxobutyronitrile[18] (**6aa**) (125 mg, 0.50 mmol), DMSO (0.4 mL), and KOH (112 mg) were mixed in a 5 mL round-bottom flask and stirred at room temperature for 30−40 min. Then, MeI (142 mg, 62 μL, 1.00 mmol) was added and the mixture was stirred for another 30−40 min (TLC control). The reaction was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (4 × 15 mL). Next, the solution was evaporated and purified by column chromatography (eluting with ethyl acetate/hexane 1:3 v/v). Yield 70 mg (0.28 mmol, 56%). All physical data were identical to those previously described.[23] The title compound was obtained as a yellow amorphous solid, R_f 0.25 (EtOAc/hexane, 1:2). ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 7.83 (dt, J = 8.1, 1.0 Hz, 1H), 7.76−7.72 (m, 2H), 7.61−7.55 (m, 1H), 7.55−7.49 (m, 2H), 7.45 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 3.31 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 188.9, 153.8, 140.9, 139.1, 131.9, 129.1, 128.7 (2C), 128.6 (2C), 121.6, 121.3, 120.0, 117.3, 110.9, 33.9; FTIR (film, NaCl, cm^{-1}): 1701, 1612, 1494, 1470, 1453, 1427, 1371, 1323, 1294, 1253, 1094; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{16}H_{13}NNaO_2$ 274.0838; found 274.0834 (1.6 ppm).

*Typical Procedure G for the Preparation of 2-Aryloyl-3-hydroxyindoles **11** from N-Alkylated 4-(2-aminophenyl)-4-oxobutyronitriles **10**.* 4-(2-(Methylamino)phenyl)-2-phenyl-4-oxobutyronitrile[18] (**10da**) (125 mg, 0.05 mmol), DMSO (0.4 mL), and KOH (112 mg) were mixed in a 5 mL round-bottom flask and stirred at room temperature for 30−40 min. Next, AcOH (0.2 mL) was added and the mixture was stirred for another 30 min. The reaction was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (4 × 15 mL). Next, the solution was evaporated and purified by column chromatography (eluting with ethyl acetate/hexane 1:3 v/v). Yield 77 mg (0.31 mmol, 61%). The isolated sample was identical to that obtained via typical procedure F. In a single case, we managed to isolate an intermediate product (**7da**) by quenching the reaction after 5 min. Yield 20 mg (0.08 mmol, 15%).

*Typical Procedure H for the Preparation of 2-Aryloyl-3-hydroxyindoles **11** from 4-(2-Aminophenyl)-4-oxobutyronitriles **6** (Scale-Up Procedure).* 4-(2-Aminophenyl)-2-phenyl-4-oxobutyronitrile[18] (**6aa**) (500 mg, 2.00 mmol), DMSO (1.6 mL), and KOH (448 mg, 8.00 mmol) were mixed in a 25 mL round-bottom flask and left for 30−40 min under stirring at room temperature. Then, MeI (568 mg, 248 μL, 4.00 mmol) was added and the mixture was left for another 30−40 min (TLC control). The reaction was diluted with H_2O (80 mL) and extracted with CH_2Cl_2 (4 × 60 mL). Next, the solution was evaporated and purified by column chromatography (eluting with ethyl acetate/hexane 1:3 v/v). Yield 296 mg (1.18 mmol, 59%). The isolated sample was identical to that obtained via typical procedure F.

*1-Methyl-2-(4-methoxybenzoyl)-3-hydroxyindole (**11de**).* This compound was prepared via typical procedure F employing 4-(2-aminophenyl)-2-(4-methoxyphenyl)-4-oxobutanenitrile[18] (**6ae**) (140 mg, 0.50 mmol) and benzyl bromide (94 mg, 65 μL, 0.55 mmol) with yield 101 mg (0.36 mmol, 72%). Alternatively, this compound was prepared by typical procedure G employing 2-(4-methoxyphenyl)-4-(2-(methylamino)phenyl)-4-oxobutanenitrile (**10de**) (147 mg, 0.50 mmol) with yield 108 mg (0.39 mmol, 77%). Eluent for preparative column chromatography:EtOAc/hexane, 1:4. The titled compound was obtained as a brown amorphous solid, R_f 0.32 (EtOAc/hexane, 1:4). ^1H NMR (400 MHz, DMSO-d_6) δ

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10.46 (s, 1H), 7.82 (dt, J = 8.0, 1.0 Hz, 1H), 7.80−7.74 (m, 2H), 7.45 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.26 (d, J = 8.5 Hz, 1H), 7.13 (ddd, J = 7.9, 7.0, 0.8 Hz, 1H), 7.06−6.99 (m, 2H), 3.90 (s, 3H), 3.38 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 187.8, 162.9, 153.2, 141.0, 131.5, 131.3 (2C), 128.8, 121.8, 121.2, 120.1, 117.8, 114.0 (2C), 111.1, 55.6, 34.2; FTIR (film, NaCl, cm^{-1}): 1725, 1680, 1595, 1513, 1465, 1427, 1304, 1253, 1173, 1108, 1029; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{17}H_{15}NNaO_3$ 304.0944; found 304.0945 (−0.2 ppm).

*1-Benzyl-2-benzoyl-3-hydroxyindole (**11ea**).* This compound was prepared by typical procedure F employing 4-(2-aminophenyl)-4-oxo-2-phenylbutanenitrile[18] (**6aa**) (125 mg, 0.50 mmol) and benzyl bromide (94 mg, 65 μL, 0.55 mmol) with yield 77 mg (0.24 mmol, 47%). Alternatively, this compound was prepared by typical procedure G employing 4-(2-(benzylamino)phenyl)-4-oxo-2-phenylbutanenitrile (**10ea**) (170 mg, 0.50 mmol) with yield 78 mg (0.24 mmol, 48%). Eluent for preparative column chromatography: EtOAc/hexane, 1:3. The title compound was obtained as a yellow amorphous solid, R_f 0.29 (EtOAc/hexane, 1:2). ^1H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.88 (dt, J = 8.1, 1.0 Hz, 1H), 7.68−7.62 (m, 2H), 7.57−7.52 (m, 1H), 7.42 (ddd, J = 8.6, 6.9, 1.3 Hz, 3H), 7.28−7.24 (m, 1H), 7.14 (tt, J = 7.7, 6.2 Hz, 4H), 6.63−6.57 (m, 2H), 5.04 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 189.2, 154.3, 140.6, 139.0, 137.2, 131.8, 129.2, 128.6 (2C), 128.5 (2C), 128.4 (2C), 127.5, 126.2 (2C), 121.4, 120.4, 120.3, 117.9, 111.7, 49.2; FTIR (film, NaCl, cm^{-1}): 3065, 1737, 1619, 1590, 1574, 1523, 1494, 1448, 1342, 1287, 1183, 1120, 1019; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{22}H_{17}NNaO_2$ 350.1151; found 350.1156 (−1.3 ppm).

*4-Phenyl-5H-pyridazino[4,3-b]indol-3-amine (**2aa**). Typical Procedure I for the Preparation of 5H-Pyridazino[4,3-b]indol-3-amines **23** from 4-(2-Aminophenyl)-4-oxobutyronitriles **6**.* This procedure is a modified one-pot version of the method reported in the literature.[15] 4-(2-Aminophenyl)-2-phenyl-4-oxobutyronitrile[18] (**6aa**) (250 mg, 1.00 mmol), DMSO (0.8 mL), and KOH (224 mg) were mixed in a 25 mL round-bottom flask and stirred at room temperature for 30−40 min. Then, acetic acid (8.5 mL) and hydrazine hydrate (98%, 4 mL) were added and the reaction mixture was heated under reflux for 4 h. After this period, the solution was allowed to cool down and then poured down into 100 mL of crushed ice. The mixture was extracted with CH_2Cl_2 (4 × 15 mL). Next, the solution was evaporated and purified by column chromatography (eluting with acetone). Additional purification can be achieved by recrystallization from EtOH of *i*-PrOH. The title compound was obtained as a white solid, mp 306.5−308.9 °C (*i*-PrOH), lit[15] mp 308−310 °C, R_f 0.34 (acetone). Yield 148 mg (0.57 mmol, 57%). ^1H NMR spectra was identical to that reported in the literature.[15] ^1H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.65−7.56 (m, 4H), 7.55−7.48 (m, 1H), 7.43 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.23 (ddd, J = 8.0, 6.9, 1.3 Hz, 1H), 5.72 (s, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 155.6, 142.7, 141.8, 134.3, 131.9, 129.6 (2C), 129.4 (2C), 128.5, 127.7, 120.8, 120.5, 119.5, 111.7, 103.8; FTIR (film, NaCl, cm^{-1}): 3483, 3277, 3118, 1624, 1540, 1459, 1441, 1383, 1356, 1230, 1244, 1160, 1145; HRMS (ESI TOF) m/z: $(M + H)^+$ calc'd for $C_{16}H_{13}N_4$ 261.1135; found 261.1131 (1.4 ppm).

*4-(p-Tolyl)-5H-pyridazino[4,3-b]indol-3-amine (**2ab**).* This compound was prepared via typical procedure I employing 4-(2-aminophenyl)-4-oxo-2-(p-tolyl)butanenitrile[18] (**6ab**) (264 mg, 1.00 mmol). The title compound was obtained as a white solid, mp 313.7−316.0 °C (*i*-PrOH), lit[15] mp 210−212 °C (EtOH), R_f 0.34 (acetone). Yield 151 mg (0.55 mmol, 55%). ^1H NMR spectra were identical to those reported in the literature.[15] ^1H NMR (400 MHz, DMSO-d_6) δ 10.97 (s, 1H), 8.15 (d, J = 7.7 Hz, 1H), 7.63−7.32 (m, 6H), 7.22 (t, J = 7.3 Hz, 1H), 5.69 (s, 2H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 155.7, 142.6, 141.8, 137.8, 134.4, 130.1 (2C), 129.3 (2C), 128.8, 127.7, 120.8, 120.4, 119.5, 111.7, 103.9, 21.0.; FTIR (film, NaCl, cm^{-1}): 3460, 3289, 3110, 1612, 1536, 1457, 1379, 1352, 1302, 1242, 1151; HRMS (ESI TOF) m/z: $(M + Na)^+$ calc'd for $C_{17}H_{15}N_4$ 275.1291; found 275.1292 (−0.2 ppm).

*4-(4-Methoxyphenyl)-5H-pyridazino[4,3-b]indol-3-amine (**2ae**).* This compound was prepared via typical procedure I employing 4-(2-aminophenyl)-2-(4-methoxyphenyl)-4-oxobutanenitrile[18] (**6ae**) (280 mg, 1.00 mmol). The title compound was obtained as a white solid, mp 293.1−294.6 °C (EtOH), lit[15] mp 289−290 °C, R_f 0.28 (acetone). Yield 180 mg (0.62 mmol, 62%). ^1H NMR spectra was identical to those reported in the literature.[15] ^1H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 5.68 (s, 2H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 159.3, 155.9, 142.6, 141.8, 134.5, 130.7 (2C), 127.6, 123.7, 120.9, 120.4, 119.5, 115.0 (2C), 111.7, 103.8, 55.3; FTIR (film, NaCl, cm^{-1}): 3337, 3142, 3023, 2967, 1771, 1762, 1505, 1430, 1356, 1252, 1154, 1108; HRMS (ESI TOF) m/z: $(M + H)^+$ calc'd for $C_{17}H_{15}N_4O$ 291.1240; found 291.1236 (1.7 ppm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c01238.

Spectral data: ^1H, $^{13}C\{^1H\}$ NMR, and HRMS spectral charts and X-ray crystallography data (PDF)

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Notes

The authors declare no competing financial interest.

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