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# Homogeneous and Stereoselective Copper(II)-Catalyzed Monohydration of Methylenemalononitriles to 2-Cyanoacrylamides

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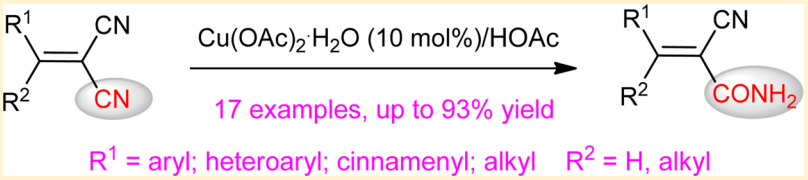
Supporting Information




**ABSTRACT:** A facile and efficient route for the homogeneous and highly stereoselective monohydration of substituted methylenemalononitriles to (*E*)-2-cyanoacrylamides catalyzed by copper(II) acetate monohydrate in acetic acid containing 2% water is described, and a mechanism is proposed. The protocol has proved to be suitable for the monohydration of dicyanobenzenes and 2-substituted malononitriles.

## INTRODUCTION

The transformation based on hydration of nitriles to amides has attracted considerable research attention in the past few decades since functionalized amides not only can be used as versatile building blocks in synthetic chemistry but also exhibit pharmacological interest.[1] The hydration of nitriles can conventionally be achieved using strong acid or base catalysis.[2] However, the reaction is mostly not possible to stop at the amide stage, and further hydrolysis to the acid often occurs. Meanwhile, the acid- or base-sensitive functionalities are usually affected or lost during the harsh reaction conditions. To overcome these intrinsic problems associated with the hydration process, tremendous efforts have been made in the catalytic hydration of nitriles.[3] For instance, Yamada's NHase catalyst,[4] Parkins's platinum complexes,[5] Murahashi's ruthenium system,[6] and other transition-metal catalysts[7] were employed in hydration of nitriles and exhibited remarkable activities in many cases.

Even though some significant advances have been achieved in catalytic hydration, there are only a few reports on the hydration of dinitriles. Breuilles and co-workers found that treatment of $\beta$-hydroxyglutarodinitrile with $MnO_2/SiO_2$ for one week at room temperature could result in the corresponding monoamides in 55% yield (76% conversion).[8] Grigg and co-workers investigated the hydration of substituted malononitriles using $KF-Al_2O_3$ in *t*-BuOH and obtained the monohydrated products in 57−75% yields.[9] A heterogeneous catalytic hydration of dinitriles described by Kiss revealed that a mixture of mono- and diamides was formed when adiponitrile and acetaldoxime were treated with molecular sieves modified with copper(II).[10] Under microwave (MW) irradiation conditions in aqueous media, dihydration of dicyano derivatives with ruthenium nanocatalysts was achieved.[11] Very recently, a regiospecific $MnO_2$-catalyzed hydration process of methylenemalononitriles with oximes into cyanoacrylamides was reported.[12] Actually, hydration of dinitriles is a matter of importance as there are equal possibilities of mono- and dihydration involving cooperative activation of nitrile and water with two or more metallic centers.

During the course of our studies on malononitrile and its derivatives, we achieved efficient one-pot synthesis of polysubstituted benzenes[13] and pyridines.[14] In connection with this previous work, we are interested in the hydration of these substituted malononitriles under varied conditions. After a series of research, we developed a facile and efficient approach for the homogeneous and highly stereoselective monohydration of substituted 2-methylenemalononitriles to 2-cyanoacrylamides catalyzed by copper(II) acetate monohydrate in acetic acid. Herein, we report our results and the mechanism involved in the process.

## RESULTS AND DISCUSSION

The substrates, 2-methylenemalononitriles **1a−q**, with two cyano groups on the same $sp^2$ carbon atom were prepared by condensation of malononitrile with various aldehydes or ketones according to the published procedure.[15] We selected 2-benzylidenemalononitrile (**1a**) as the model compound to examine its behavior under different conditions. Initially, the substrate **1a** and copper(II) acetate [$Cu(OAc)_2$; 0.2 equiv] were subjected to water in the presence of 10 mol % tetrabutylammonium bromide (TBAB) at room temperature, but no reaction was observed (Table 1, entry 1). When the

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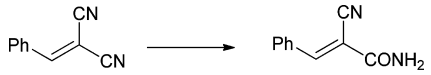
**Table 1. Hydration of 1a under Different Conditions**[a]




**1a** **(*E*)-2a**

| entry | catalyst (concn, equiv) | solvent | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|---|
| 1 | $Cu(OAc)_2$ (0.2) | $H_2O$ | rt | 8.0 | nr |
| 2 | $Cu(OAc)_2$ (0.2) | HOAc | 80 | 8.0 | 64 |
| 3 | $Cu(OAc)_2·H_2O$ (0.2) | HOAc | 80 | 8.0 | 76 |
| 4 | $Cu(OAc)_2·H_2O$ (0.2) | THF | reflux | 8.0 | nr |
| 5 | $Cu(OAc)_2·H_2O$ (0.2) | toluene | 80 | 8.0 | nr |
| 6 | $CuCl_2·2H_2O$ (0.2) | HOAc | 80 | 8.0 | 73 |
| 7 | $CuCl_2$ (0.2) | HOAc | 80 | 12.0 | 71 |
| 8 | $CuSO_4·5H_2O$ (0.2) | HOAc | 80 | 12.0 | 62 (25)[b] |
| 9 | $FeCl_2·4H_2O$ (0.2) | HOAc | 80 | 6.0 | nr |
| 10 | $CuBr_2$ (0.2) | HOAc | 80 | 6.0 | nr |
| 11 | $Cu(OAc)_2·H_2O$ (0.2) | HOAc[c] | 80 | 8.0 | 67 (23)[b] |
| 12 | $Cu(OAc)_2·H_2O$ (0.2) | HOAc[d] | 80 | 6.0 | 82 |
| 13 | $Cu(OAc)_2·H_2O$ (0.2) | HOAc[d] | 100 | 5.0 | 80 |
| 14 | $Cu(OAc)_2·H_2O$ (0.2) | HOAc[d] | 60 | 12.0 | 55 (38)[b] |
| 15 | $Cu(OAc)_2·H_2O$ (0.1) | HOAc[d] | 80 | 6.0 | 81 |
| 16 | $Cu(OAc)_2·H_2O$ (0.05) | HOAc[d] | 80 | 6.0 | 48 (43)[b] |
| 17 | | HOAc[d] | 80 | 12.0 | nr |

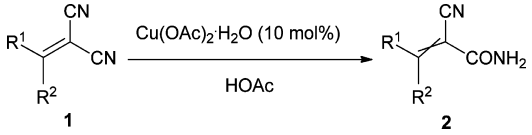
[a]Reagents and conditions: **1a** (1.0 mmol), solvent (10.0 mL). [b]Recovery of **1a** in parentheses. [c]Treated with acetic anhydride (v/v, 1:10) under reflux for 3.0 h. [d]Containing 2% water.

mixture was conducted at 80 °C for 8.0 h, retrocondensation reaction of **1a** took place to give back malononitrile and benzaldehyde. To our delight, the reaction of **1a** with $Cu(OAc)_2$ (0.2 equiv) could proceed in acetic acid at 80 °C to afford (*E*)-2-cyano-3-phenylacrylamide [(*E*)-**2a**] (Table 1, entry 2).[16a]

The optimization of the reaction conditions, including reaction solvents, catalysts, reaction temperature, and the feed ratio of the catalysts, was then investigated. It was found that (*E*)-**2a** could be obtained in 76% yield when copper(II) acetate monohydrate, $Cu(OAc)_2·H_2O$, was employed in the reaction system (Table 1, entry 3). However, no reaction occurred when **1a** was treated with $Cu(OAc)_2·H_2O$ (0.2 equiv) in tetrahydrofuran (THF) under reflux or toluene at 80 °C for 12.0 h (Table 1, entries 4 and 5). Other divalent metal salts, such as $CuCl_2·2H_2O$, $CuCl_2$, $CuSO_4·5H_2O$, $FeCl_2·4H_2O$, and $CuBr_2$, were also attempted but were less active than $Cu(OAc)_2·H_2O$ (Table 1, entries 6–8) or inert to substrate **1a** (Table 1, entries 9 and 10). It was interesting to note that use of the dried acetic acid would result in a low conversion of **1a** (Table 1, entry 11), whereas in the acetic acid containing 2% water the yield of (*E*)-**2a** reached 82% (Table 1, entry 12). Higher reaction temperature had no significant influence on the reaction of **1a** (Table 1, entry 13), but lower reaction temperature, for example, at 60 °C, would result in low conversion and prolonged reaction time (Table 1, entry 14). Upon a decrease of the amount of $Cu(OAc)_2·H_2O$ to 0.1 equiv, the reaction of **1a** could furnish (*E*)-**2a** in 81% yield (Table 1, entry 15). However, a further decrease of the amount of $Cu(OAc)_2·H_2O$ to 0.05 equiv would lead to the incomplete hydration of **1a** (Table 1, entry 16). Without any catalyst, the hydration of **1a** could not proceed in the acetic acid containing 2% water at 80 °C for even 12.0 h (Table 1, entry 17).

Under the conditions as for (*E*)-**2a** in Table 1, entry 15, a series of reactions of 2-methylenemalononitriles **1b–q** were carried out, and some of the results are summarized in Table 2.

**Table 2. Monohydration of 2-Methylenemalononitriles 1 to 2-Cyanoacrylamides 2**[a]




**1** **2**

| entry | 1 | $R^1$ | $R^2$ | 2 | yield (%) |
|---|---|---|---|---|---|
| 1 | **1a** | Ph | H | (*E*)-**2a**[16a] | 81 |
| 2 | **1b** | 4-$ClC_6H_4$ | H | (*E*)-**2b**[16a] | 89 |
| 3 | **1c** | 4-$MeOC_6H_4$ | H | (*E*)-**2c**[16b] | 84 |
| 4 | **1d** | 4-$MeC_6H_4$ | H | (*E*)-**2d**[16a] | 83 |
| 5 | **1e** | 3-$MeOC_6H_4$ | H | (*E*)-**2e**[16a] | 92 |
| 6 | **1f** | 3-$MeC_6H_4$ | H | (*E*)-**2f**[16a] | 86 |
| 7 | **1g** | 3-$NO_2C_6H_4$ | H | (*E*)-**2g**[16c] | 93 |
| 8 | **1h** | 2-$ClC_6H_4$ | H | (*E*)-**2h**[16a] | 90 |
| 9 | **1i** | 2-$NO_2C_6H_4$ | H | (*E*)-**2i**[16d] | 87 |
| 10 | **1j** | 2-thienyl | H | (*E*)-**2j**[16b] | 91 |
| 11 | **1k** | $C_6H_5CH{=}CH$ | H | (*E*)-**2k**[16e] | 79 |
| 12 | **1l** | 4-$ClC_6H_4CH{=}CH$ | H | (*E*)-**2l** | 82 |
| 13 | **1m** | 4-$MeOC_6H_4CH{=}CH$ | H | (*E*)-**2m** | 86 |
| 14 | **1n** | $-(CH_2)_5-$ | | **2n** | 54 |
| 15 | **1o** | Ph | Me | **2o**[16b,17] | 80(2:1)[b] |
| 16 | **1p** | 4-$ClC_6H_4$ | Me | (*E*)-**2p** | 46 |
| | | | | (*Z*)-**2p**[17] | 27 |
| 17 | **1q** | 4-$NO_2C_6H_4$ | Me | (*E*)-**2q** | 41 |
| | | | | (*Z*)-**2q** | 20 |

[a]Reagents and conditions: (i) **1a–n** (1.0 mmol), HOAc (10.0 mL), $H_2O$ (0.2 mL), $Cu(OAc)_2·H_2O$ (0.1 mmol), 80 °C, 6.0–10.0 h; (ii) **1o–q** (1.0 mmol), HOAc (10.0 mL), $H_2O$ (0.2 mL), $Cu(OAc)_2·H_2O$ (0.1 mmol), 100 °C, 12.0 h. [b]The ratio in parentheses is that of *E* to *Z* isomers determined by $^1H$ NMR.

The substrates **1b–m** bearing varied aryl, heteroaryl, or cinnamenyl groups $R^1$ could undergo hydration to afford the corresponding (*E*)-2-cyanoacrylamides (*E*)-**2b–m**[16] in high yields (Table 2, entries 2–13). The structure of (*E*)-**2d** was elucidated by means of X-ray single-crystal analysis (see Figure S2, Supporting Information), and these data conveniently revealed that the hydration precisely took place at the *anti*-nitrile group with reference to the aryl group in (*E*)-**2d**. In these cases, (*E*)-2-cyanoacrylamides (*E*)-**2b–m** were exclusively obtained, which suggested that the catalytic hydration proceeded in a highly stereoselective manner. 2-Cyclohexylidenemalononitrile (**1n**) could also be hydrated to monamide **2n** in 54% yield under identical conditions (Table 2, entry 14). It was worth noting that the monohydration of 2,2-disubstituted methylenemalononitriles **1o–q** could proceed at 100 °C to give a mixture of (*E*)- and (*Z*)-2-cyanoacrylamides **2o–q** with the *E* isomers as the predominant ones[16b,17] (Table 2, entries 15–17). The structure of (*E*)-**2p** was established by means of X-ray single-crystal analysis and its NMR spectra (see Figure S1, Supporting Information). The above results demonstrated the wide scope and synthetic utility of the catalytic hydration of 2-methylenemalononitriles **1**. In addition, no overhydrolysis of the nitriles to carboxylic acids was observed.

Next we intended to investigate the catalytic hydration of dicyanobenzenes **1r–t** bearing two cyano groups on the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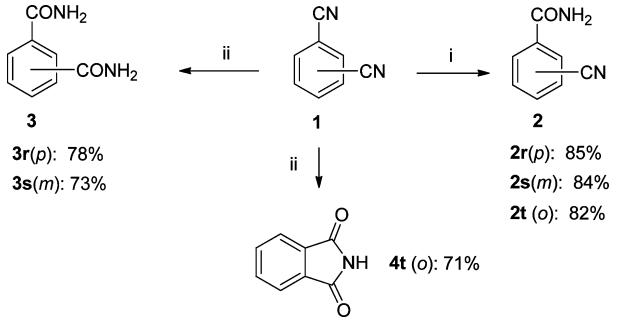
different $sp^2$ carbon atoms. The experimental results revealed that the reactions of **1r−t** performed with $Cu(OAc)_2·H_2O$ (0.1 equiv) in acetic acid containing 2% water at 100 °C could furnish the corresponding monoamides **2r−t**[11a,b] in high yields (Scheme 1). Upon treatment with $Cu(OAc)_2·H_2O$ (0.1 equiv)

**Scheme 1. Hydration of Dicyanobenzenes 1**[a]

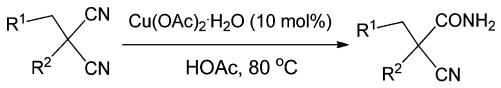



[a]Reaction conditions: (i) **1r−t** (1.0 mmol), $Cu(OAc)_2·H_2O$ (0.1 mmol), HOAc (10.0 mL), $H_2O$ (0.2 mL), 100 °C, 6.0−10.0 h; (ii) **1r−t** (1.0 mmol), HOAc (10.0 mL), $H_2O$ (0.2 mL), $Cu(OAc)_2·H_2O$ (0.1 mmol), reflux, 10.0−12.0 h.

in acetic acid containing 2% water under reflux, terephthalonitrile (**1r**) and isophthalonitrile (**1s**) could be completely converted into terephthalamide (**3r**)[11a] and isophthalamide (**3s**)[11b] in 78% and 73% yields, respectively. However, in the case of phthalonitrile (**1t**), the product phthalimide (**4t**)[18] rather than phthalamide (**3t**) was exclusively obtained in 71% yield. Notably, the selective mono- and dihydration of dicyano derivatives could be conveniently achieved by controlling the reaction temperature and time.

The catalytic hydration of 2-substituted malononitriles **1u−y** bearing two cyano groups on the same $sp^3$ carbon atom was further examined. By being subjected to acetic acid containing 2% water at 80 °C in the presence of $Cu(OAc)_2·H_2O$ (0.1 equiv), the 2-monosubstituted malononitriles **1u−w** could be easily converted into the corresponding monoamides **2u−w** in good yields (Table 3, entries 1−3). The versatility of

**Table 3. Monohydration of 2-Substituted Malononitriles 1**[a]




1 2

| entry | 1 | $R^1$ | $R^2$ | 2 | yield (%) |
|---|---|---|---|---|---|
| 1 | **1u** | $C_6H_5CO$ | H | **2u** | 76 |
| 2 | **1v** | 4-$ClC_6H_4CO$ | H | **2v** | 77 |
| 3 | **1w** | 4-$NO_2C_6H_4CO$ | H | **2w** | 72 |
| 4 | **1x** | Ph | Bn | **2x**[19] | 89 |
| 5 | **1y** | $CO_2Et$ | $CH_2CO_2Et$ | **2y** | 88 |

[a]Reagents and conditions: **1u−y** (1.0 mmol), HOAc (10.0 mL), $H_2O$ (0.2 mL), $Cu(OAc)_2·H_2O$ (0.1 mmol), 80 °C, 2.0−12.0 h.

monoamide synthesis was also evaluated by studying the reaction of 2,2-disubstituted malononitriles **1x** and **1y** under identical conditions (Table 3, entries 4 and 5). It was observed that some sensitive functionalities, such as benzoyl, ester, and $NO_2$ groups, could tolerate the catalytic hydration process and the monohydration of dinitrile could be controlled to stop at the amide stage.

To gain insight into the mechanism of hydration, the reactions of **1a** were performed with $Cu(OAc)_2$ (0.1 equiv) in HOAc-$d_4$ containing 2% water at 80 °C for 6.0 h. No deuterated product (*E*)-**2a**-*d* was obtained according to the $^1H$ NMR spectrum. The results demonstrated that the hydrogen atom of amide does not originate from acetic acid, which is different from the conventional hydration of nitriles catalyzed by Brønsted acid or strong mineral acid.[3f,20] Furthermore, the monohydration of **1a** could proceed under an atmosphere of nitrogen, which indicated that the monohydration of nitrile might not undergo a free radical process.

On the basis of the above results obtained together with those reported in the literature,[7i,j,21] a mechanism for nitrile hydration is proposed as depicted in Scheme 2. As reported by Sharrock and co-workers, in the solution of $Cu(OAc)_2·H_2O$ in acetic acid containing 2% water, the copper complex **A** is presumably formed.[22] The hydration commences from the coordination of methylenemalononitriles **1** to the divalent copper center of **A** to give intermediate **B**. The *anti*-cyano group of **1** with reference to the $R^1$ group ($R^1$ = aryl, $R^2$ = alkyl, H) is favored to coordinate to the copper center due to both electronic and steric effects.[23] The nucleophilic attack of $H_2O$ on the carbon atom of the nitrile of **B** subsequently takes place to afford intermediate **C**. The product, a monoamide of type **2**, was then formed by the tautomerization of an iminol, **D**, along with the regeneration of the copper complex **A**.

## ■ CONCLUSION

In summary, we developed a facile and efficient route for the homogeneous and stereoselective monohydration of 2-methylenemalononitriles to 2-cyanoacrylamides catalyzed by copper(II) acetate monohydrate in acetic acid containing 2% water, which was expanded to the monohydration of dicyanobenzenes and 2-substituted malononitriles. In comparison to the prior work on the hydration of dinitriles, this protocol is associated with inexpensive and easily available copper(II) catalyst, simple execution, mild conditions, good to high yields, and high selectivity, which make it most attractive for academic research and practical applications.

## ■ EXPERIMENTAL SECTION

**Materials and Methods.** All reagents were purchased from commercial sources and used without further treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. $^1H$ NMR and $^{13}C$ NMR spectra were recorded at 300 MHz (or 400 MHz) and 100 MHz, respectively, with TMS as the internal standard. IR spectra (KBr) were recorded on an FTIR spectrophotometer in the range of 400−4000 $cm^{-1}$. The petroleum ether (PE) fraction used was that boiling in the 60−90 °C range.

**Synthesis.** *Typical Procedure for the Synthesis of Monoamides 2 (2a as an Example).* A mixture of 2-benzylidenemalononitrile (**1a**) (1.0 mmol, 154 mg) and $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) $H_2O$ (0.2 mL) in HOAc (10.0 mL) was stirred at 80 °C for 6.0 h and then poured into saturated aqueous NaCl (50 mL), which was extracted with dichloromethane (3 × 20 mL). The combined organic phase was washed with water (3 × 20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether:ethyl acetate = 2:1) to give (*E*)-**2a**: yield 139 mg (81%); mp 120−122 °C; $^1H$ NMR (300 MHz, DMSO) $\delta$ = 7.55−7.60 (m, 3H), 7.82 (s, 1H), 7.94−7.97 (m, 3H), 8.21 (s, 1H); $^{13}C$ NMR (100 MHz, DMSO) $\delta$ = 106.7, 116.5, 129.2, 130.0, 131.9, 132.3, 150.7, 162.8; IR (KBr) 3398, 3313, 3161, 2218, 1670, 1597, 1371, 685 $cm^{-1}$. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.53; H, 4.66; N, 16.20.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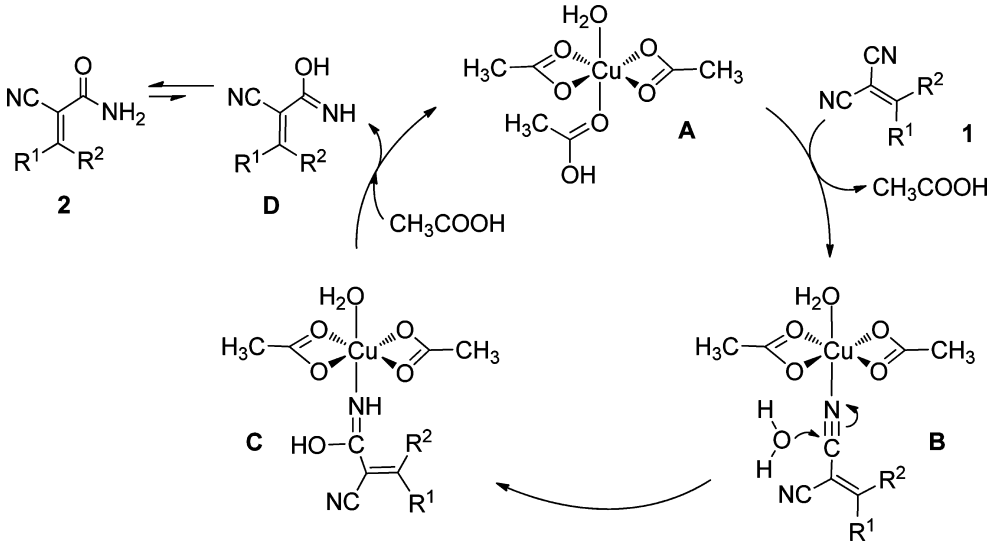
**Scheme 2. Plausible Mechanism for the Hydration of Nitriles Catalyzed by $Cu(OAc)_2 \cdot H_2O$ in Acetic Acid Containing Water**




(*E*)-**2a**–**k**, (*E*)-**2o**, (*Z*)-**2o**, (*Z*)-**2p**, **2r**–**t**, and **2x** are known compounds. For the spectral and analytical data of (*E*)-**2a**–**k** and (*E*)-**2o**, see ref 16, for those of (*Z*)-**2o** and (*Z*)-**2p**, see ref 17, for those of **2x**, see ref 19, and for those of **2r**–**t**, see ref 11.

*Data for (E)-**2b**:* yield 184 mg (89%); white solid; mp 198–200 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.57–7.61 (m, 2H), 7.79 (s, 1H), 7.91–7.93 (m, 3H), 8.16 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 107.1, 116.2, 129.2, 130.6, 131.5, 136.9, 149.2, 162.4. Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56. Found: C, 58.29; H, 3.42; N, 13.50.

*Data for (E)-**2c**:* yield 170 mg (84%); yellow solid; mp 207–209 °C; H NMR (300 MHz, DMSO) $\delta$ = 3.83 (s, 3H), 7.11 (d, $J$ = 8.7 Hz, 2H), 7.70 (s, 1H), 7.82 (s, 1H), 7.95 (d, $J$ = 8.7 Hz, 2H), 8.11 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 55.5, 102.8, 114.7, 117.0, 124.4, 132.4, 150.1, 162.5, 163.1. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.05; H, 4.96; N, 13.90.

*Data for (E)-**2d**:* yield 155 mg (83%); white solid; mp 154–156 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 2.43 (s, 3H), 6.31 (s, 1H), 6.38 (s, 1H), 7.30 (d, $J$ = 8.1 Hz, 2H), 7.86 (d, $J$ = 8.1 Hz, 2H), 8.30 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 21.1, 105.1, 116.6, 129.1, 129.7, 130.1, 142.9, 150.5, 162.8; IR (KBr) 3387, 3317, 3157, 2218, 1695, 1591, 1373, 1182, 816, 608 cm$^{-1}$. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.69; H, 5.44; N, 15.12.

Crystal data for (*E*)-**2d**: $C_{11}H_{10}N_2O$, white crystal, $M$ = 186.21, monoclinic, $P2_1/n$, $a$ = 13.4278(11) Å, $b$ = 10.9087(9) Å, $c$ = 13.4767(11) Å, $\alpha$ = 90.00°, $\beta$ = 99.6090(10)°, $\gamma$ = 90.00°, $V$ = 1946.4(3) Å$^3$, $Z$ = 8, $T$ = 293(2) K, $F_{000}$ = 858. CCDC deposition number 937685. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB21EZ, U.K.; fax (+44)1223-336-033; e-mail deposit@ccdc.cam.ac.uk).

*Data for (E)-**2e**:* yield 186 mg (92%); white solid; mp 146–148 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 3.79 (s, 3H), 7.14 (d, $J$ = 7.5 Hz, 1H), 7.43–7.51 (m, 3H), 7.82 (s, 1H), 7.94 (s, 1H), 8.15 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 55.2, 106.8, 114.7, 116.4, 118.1, 122.4, 130.3, 133.1, 150.5, 159.4, 162.6. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.07; H, 5.01; N, 13.79.

*Data for (E)-**2f**:* yield 160 mg (86%); white solid; mp 104–105 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 2.36 (s, 3H), 7.38–7.47 (m, 2H), 7.72–7.79 (m, 3H), 7.93 (s, 1H), 8.14 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 20.8, 106.4, 116.5, 127.0, 129.1, 130.6, 131.9, 133.0, 138.5, 150.6, 162.7; IR (KBr) 3472, 3298, 3148, 2218, 1707, 1603, 1385, 1373, 748 cm$^{-1}$. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.66; H, 5.38; N, 15.11.

*Data for (E)-**2g**:* yield 202 mg (93%); white solid; mp 157–159 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 7.73–7.78 (m, 1H), 7.84 (s, 1H), 7.90 (s, 1H), 8.23(s, 3H), 8.65 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 109.1, 115.7, 123.9, 126.0, 130.6, 132.3, 135.7, 147.8, 148.1, 162.0. Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.15; H, 3.26; N, 19.27.

*Data for (E)-**2h**:* yield 186 mg (90%); white solid; mp 158–160 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 7.52–7.67 (m, 3H), 7.93–8.08 (m, 3H), 8.37 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 111.0, 115.5, 127.8, 129.7, 130.0, 130.5, 133.2, 134.0, 147.1, 161.8; IR (KBr) 3421, 3350, 3231, 2212, 1678, 1578, 1570, 1383, 1169, 989, 752, 692 cm$^{-1}$. Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56. Found: C, 58.24; H, 3.44; N, 13.61.

*Data for (E)-**2i**:* yield 189 mg (87%); white solid; mp 168–170 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.77–7.80 (m, 1H), 7.84–7.95 (m, 4H), 8.26 (d, $J$ = 8.8 Hz, 1H), 8.55 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 111.7, 115.4, 125.5, 128.9, 131.0, 132.3, 135.0, 147.4, 150.2, 161.8. Anal. Calcd for $C_{10}H_7N_3O_3$: C, 55.30; H, 3.25; N, 19.35. Found: C, 55.51; H, 3.24; N, 19.44.

*Data for(E)-**2j**:* yield 162 mg (91%); yellow solid; mp 153–154 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 7.30–7.33 (m, 1H), 7.72 (s, 1H), 7.83 (s, 1H), 7.87 (d, $J$ = 3.6 Hz, 1H), 8.09 (d, $J$ = 5.1 Hz, 1H), 8.41 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 102.1, 116.7, 128.5, 134.9, 135.8, 137.7, 143.5, 162.6; IR (KBr) 3367, 3173, 1659, 1624, 1578, 1402, 1298, 793, 685 cm$^{-1}$. Anal. Calcd for $C_8H_6N_2OS$: C, 53.92; H, 3.39; N, 15.72. Found: C, 54.13; H, 3.37; N, 15.66.

*Data for (E)-**2k**:* yield 157 mg (79%); orange solid; mp 150–152 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 7.17 (dd, $J_1$ = 15.3 Hz, $J_2$ = 11.4 Hz, 1H), 7.41–7.45 (m, 4H), 7.67–7.68 (m, 3H), 7.85 (s, 1H), 7.99 (d, $J$ = 11.4 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 107.8, 115.4, 123.0, 128.2, 129.1, 130.6, 134.9, 146.8, 151.3, 162.5; IR (KBr) 3466, 3410, 3157, 2210, 1695, 1576, 1385, 978, 810 cm$^{-1}$. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.45; H, 5.12; N, 14.05

*Data for (E)-**2l**:* yield 191 mg (82%); yellow solid; mp 200–202 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.17 (dd, $J_1$ = 15.2 Hz, $J_2$ = 11.2 Hz, 1H), 7.42 (dd, $J$ = 15.2 Hz, 1H), 7.50 (d, $J$ = 8.4 Hz, 2H), 7.65 (s, 1H), 7.72 (d, $J$ = 8.4 Hz, 2H), 7.83 (s, 1H), 7.96 (d, $J$ = 11.2 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 108.2, 115.3, 123.7, 129.1, 129.9, 133.8, 135.0, 145.2, 150.9, 162.4; IR (KBr) 3450, 3360, 3151, 2210, 1686, 1572, 1389, 1256, 822, 748 cm$^{-1}$. Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 62.22; H, 3.93; N, 11.99.

*Data for (E)-**2m**:* yield 196 mg (86%); yellow solid; mp 190–191 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ = 3.81 (s, 3H), 7.00–7.06 (m, 3H), 7.38 (dd, $J$ = 15.2 Hz, 1H), 7.06 (s, 1H), 7.65 (d, $J$ = 8.8 Hz, 2H), 7.75 (s, 1H), 7.94 (d, $J$ = 11.2 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 55.4, 105.9, 114.6, 115.7, 120.7, 127.5, 130.2, 146.9, 151.8, 161.4, 162.8; IR (KBr) 3391, 3317, 3157, 2218, 1701, 1578, 1375, 1207, 754,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700 $cm^{-1}$. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.18; H, 5.26; N, 12.34.

*Data for* ***2n:*** yield 89 mg (54%); orange solid; mp 100−102 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 1.64−1.82 (m, 6H), 2.60 (t, $J$ = 6.0 Hz, 2H), 2.94 (t, $J$ = 6.0 Hz, 2H), 6.08 (s, 1H), 6.17 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 25.2, 27.7, 28.1, 31.0, 36.5, 102.1, 116.4, 162.9, 117.2; Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.47; H, 7.38; N, 16.97.

*Data for a mixture of (E)-***2o** *and (Z)-***2o:** $E$:$Z$ = 2:1; yield 149 mg (80%); orange solid; mp 125−129 °C; $^1$H NMR ($Z$ isomer) (300 MHz, DMSO) $\delta$ = 2.40 (s, 3H), 7.39 (s, 5H), 7.51 (s, 1H), 7.74 (s, 1H); $^1$H NMR ($E$ isomer) (300 MHz, DMSO) $\delta$ = 2.34 (s, 3H), 7.49 (s, 5H), 7.82 (s, 1H), 8.08 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 22.0, 23.9, 108.5, 109.2, 116.7, 116.9, 127.1, 128.3, 128.6, 129.5, 129.7, 138.1, 139.3, 158.7, 160.8, 163.3, 163.5. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.66; H, 5.44; N, 15.13.

*Data for (E)-***2p:** yield 101 mg (46%); yellow solid; mp 161−163 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 2.33 (s, 3H), 7.53 (d, $J$ = 8.7 Hz, 2H), 7.57 (d, $J$ = 8.7 Hz, 2H), 7.86 (s, 1H), 8.09 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 21.9, 109.0, 116.8, 128.7, 129.2, 134.5, 138.1, 159.7, 163.3. Anal. Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 59.67; H, 4.15; N, 12.75.

Crystal data for (*E*)-**2p**: $C_{11}H_9ClN_2O$, white crystal, $M$ = 220.65, monoclinic, $P2_1/n$, $a$ = 18.014 Å, $b$ = 11.966 Å, $c$ = 25.055 Å, $\alpha$ = 90.00°, $\beta$ = 98.57°, $\gamma$ = 90.00°, $V$ = 5340.6 Å$^3$, $Z$ = 20, $T$ = 273(2) K, $F_{000}$ = 2280. CCDC deposition number 938999. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB21EZ, U.K.; fax (+44)1223−336−033; e-mail deposit@ccdc.cam.ac.uk).

*Data for (Z)-***2p:** yield 60 mg (27%); yellow solid; mp 135−136 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 2.39 (s, 3H), 7.39 (d, $J$ = 8.7 Hz, 2H), 7.49 (d, $J$ = 8.7 Hz, 2H), 7.56 (s, 1H), 7.80 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 23.8, 109.6, 116.5, 128.4, 129.0, 134.3, 136.9, 157.7, 163.1. Anal. Calcd for $C_{11}H_9ClN_2O$: C, 59.88; H, 4.11; N, 12.70. Found: C, 60.04; H, 4.14; N, 12.66.

*Data for (E)-***2q:** yield 95 mg (41%); orange solid; mp 134−136 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 2.37 (s, 3H), 7.77 (d, $J$ = 8.7 Hz, 2H), 7.93 (s, 1H), 8.16 (s, 1H), 8.34 (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 21.8, 110.1, 116.2, 123.8, 128.7, 145.7, 147.9, 158.8, 162.8. $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.38; H, 3.90; N, 18.09.

*Data for (Z)-***2q:** yield 46 mg (20%); orange solid; mp 193−196 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 2.43 (s, 3H), 7.60−7.63 (m, 3H), 7.87(s, 1H), 8.26 (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 24.0, 110.9, 116.1, 123.4, 128.5, 144.9, 147.7, 157.6, 162.5. Anal. Calcd for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.17. Found: C, 57.40; H, 3.93; N, 18.10.

*Data for* ***2r:*** yield 124 mg (85%); white solid; mp 215−217 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 7.69 (s, 1H), 7.95 (d, $J$ = 8.4 Hz, 2H), 8.02 (d, $J$ = 8.4 Hz, 2H), 8.22 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 113.6, 118.3, 128.2, 132.3, 138.2, 166.4; IR (KBr) 3358, 3175, 2361, 1637, 1418, 1290, 748, 700 $cm^{-1}$. Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.58; H, 4.16; N, 19.11.

*Data for* ***2s:*** yield 123 mg (84%); white solid; mp 228−230 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 7.67−7.72 (m, 2H), 8.01 (d, $J$ = 7.8 Hz, 1H), 8.18 (d, $J$ = 7.8 Hz, 2H), 8.28 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 111.4, 118.3, 129.7, 131.0, 132.2, 134.7, 135.3, 165.9; IR (KBr) 3443, 3362, 3294, 3171, 2230, 1705, 1618, 1560, 1414, 1398, 860, 548 $cm^{-1}$. Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.54; H, 4.16; N, 19.24.

*Data for* ***2t:*** yield 120 mg (82%); white solid; mp 179−181 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 7.64−7.70 (m, 1H), 7.74−7.83 (m, 3H), 7.92 (d, $J$ = 7.5 Hz, 1H), 8.18 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 110.2, 117.7, 128.1, 130.8, 132.7, 134.2., 138.7, 166.8; IR (KBr) 3420, 3306, 3155, 2231, 1705, 1628, 1396, 906, 787, 673 $cm^{-1}$. Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.63; H, 4.10; N, 19.11.

*Data for* ***2u:*** yield 154 mg (76%); white solid; mp 153−155 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 3.64 (dd, $J_1$ = 18.3 Hz, $J_2$ = 6.0 Hz, 1H), 3.82 (dd, $J_1$ = 18.3 Hz, $J_2$ = 6.0 Hz, 1H), 4.04 (t, $J$ = 6.0 Hz, 1H), 5.74 (s, 1H), 6.38 (s, 1H), 7.48−7.53 (m, 2H), 7.61−7.66 (m, 1H), 7.96−7.98 (m, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 32.1, 37.7, 118.9, 128.1, 128.9, 133.8, 135.6, 165.9, 195.9; IR (KBr) 3412, 3325, 3196, 2206, 1645, 1566, 1400, 1173, 1065, 754 $cm^{-1}$. Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.52; H, 5.00; N, 13.90.

*Data for* ***2v:*** yield 182 mg (77%); yellow solid; mp 169−170 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 3.59−3.78 (m, 2H), 4.07 (t, $J$ = 6.9 Hz, 1H), 7.55 (s, 1H), 7.62 (d, $J$ = 8.4 Hz, 2H), 7.93 (s, 1H), 8.02 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 31.9, 37.6, 118.7, 128.9, 130.0, 134.2, 138.6, 165.7, 194.9. Anal. Calcd for $C_{11}H_9ClN_2O_2$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.68; H, 3.85; N, 11.92.

*Data for* ***2w:*** yield 178 mg (72%); yellow solid; mp 189−190 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 3.69−3.86 (m, 2H), 4.10 (t, $J$ = 6.6 Hz, 1H), 7.58 (s, 1H), 7.95 (s, 1H), 8.25 (d, $J$ = 8.7 Hz, 2H), 8.35 (d, $J$ = 8.7 Hz, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 31.8, 37.8, 117.3, 122.8, 128.6, 140.1, 149.9, 164.8, 194.4. Anal. Calcd for $C_{11}H_9N_3O_4$: C, 53.44; H, 3.67; N, 17.00. Found: C, 53.23; H, 3.66; N, 17.06.

*Data for* ***2x:*** yield 235 mg (89%); white solid; mp 168−169 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 3.08 (d, $J$ = 13.5 Hz, 2H), 3.39 (d, $J$ = 7.8 Hz, 2H), 7.31 (s, 10H), 7.60 (s, 1H), 7.66 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 41.9, 54.2, 119.7, 127.3, 128.2, 130.0, 135.3, 168.2. Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.01; H, 6.13; N, 10.64.

*Data for* ***2y:*** yield 223 mg (88%); white solid; mp 104−106 °C; $^1$H NMR (300 MHz, DMSO) $\delta$ = 1.18 (t, $J$ = 7.2 Hz, 6H), 3.02 (s, 4H), 4.09 (q, $J$ = 7.2 Hz, 4H), 7.66 (s, 1H), 7.68 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 13.5, 38.7, 42.0, 60.2, 118.8, 166.7, 168.1. Anal. Calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.45; H, 6.31; N, 10.90.

*Typical Procedure for the Synthesis of* ***3*** *and* ***4*** *(****3r*** *as an Example).* To a solution of terephthalonitrile (**1r**) (1.0 mmol, 128 mg) and $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in HOAc (10.0 mL) was added $H_2O$ (0.2 mL) in one portion. The mixture was stirred at reflux for 12.0 h and then poured into saturated aqueous NaCl (50 mL). The crude product was collected by filtration, washed with $H_2O$, and dried in vacuo to give pure product **3r**: yield 128 mg (78%); mp 331−333 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.48 (s, 2H), 7.93 (s, 4H), 8.06 (s, 2H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 127.7, 136.9, 167.6. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.71; H, 4.89; N, 17.02.

**3r**, **3s**, and **4t** are known compounds. For the spectral and analytical data of **3r** and **3s**, see ref 11, and for those of **4t**, see ref 18.

*Data for* ***3s:*** yield 120 mg (73%); white solid; mp 279−280 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.53 (s, 3H), 8.04 (s, 2H), 8.13 (s, 2H), 8.45 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 127.0, 128.5, 130.4, 134.5, 168.0. Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.45; H, 4.93; N, 17.11.

*Data for* ***4t:*** yield 104 mg (71%); white solid; mp 232−234 °C; $^1$H NMR (400 MHz, DMSO) $\delta$ = 7.78 (s, 4H), 11.30 (s, 1H); $^{13}$C NMR (100 MHz, DMSO) $\delta$ = 122.8, 132.6, 134.2, 169.1. Anal. Calcd for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.10; H, 3.41; N, 9.48.

## ■ ASSOCIATED CONTENT

### Supporting Information

X-ray single-crystal analysis of compounds (*E*)-**2d** and (*E*)-**2p**, $^1$H NMR and $^{13}$C NMR spectra for compounds **2**−**4**, and CIF files of crystallographic data for compounds (*E*)-**2d** and (*E*)-**2p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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